the action of nitric acid in the presence of, for example, sulfuric acid, followed by reduction of the nitro group with, for example, hydrogen over palladium on carbon, affords a 7-amino-1,2,3,4-tetrahydroquinoline of structure **72A**. A Knorr cyclization with a β-keto ester effected by, for example, zinc chloride, affords a compound of structure **73A**. A compound of structure **73A** may be further transformed into a compound of structure **74A** by alkylation of the nitrogen atom, which can be accomplished in one of two ways. Treatment of a compound of structure **73A** with a base, such as sodium hydride, and an alkylating agent, such as benzyl bromide, affords a compound of structure **74A**. Alternatively, treatment of a compound of structure **73A** with an aldehyde, for example acetaldehyde or paraformaldehyde, in the presence of a reducing agent, for example sodium cyanoborohydride or sodium (triacetoxy)borohydride, affords a compound of structure **74A**.

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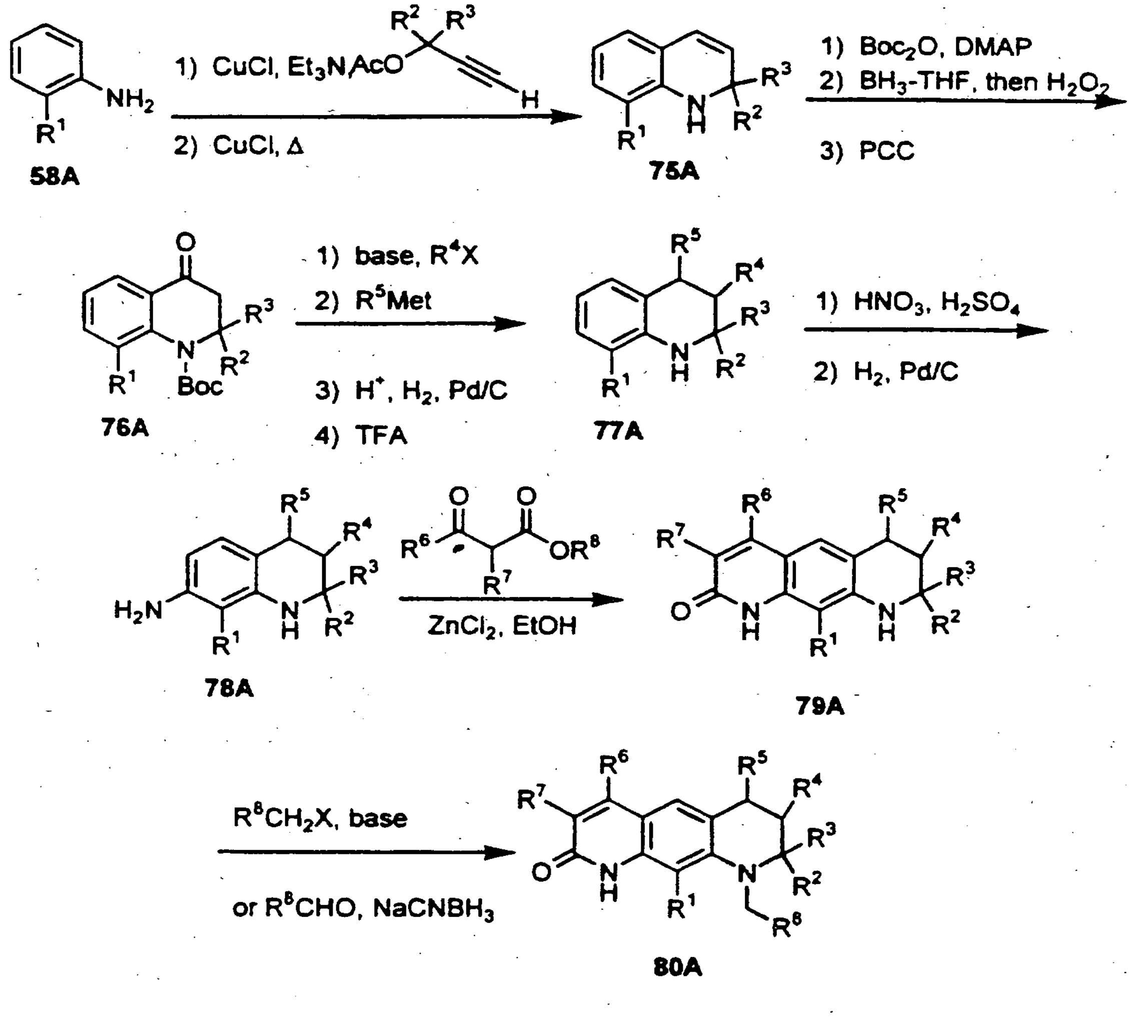
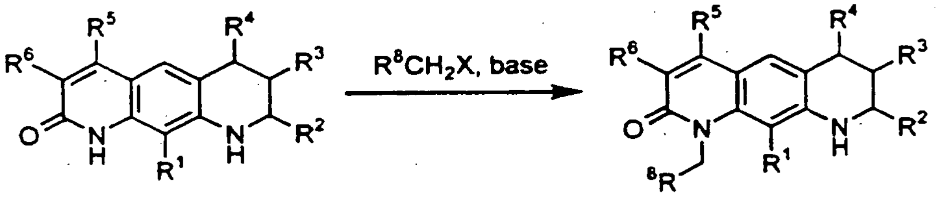
Scheme LIII



The process of **Scheme LIII** begins with the reaction of an aniline (structure **58A**) with a propargyl acetate in the presence of a copper salt such as copper(I) chloride to afford a compound of structure **75A**. The nitrogen atom is then protected by treatment with a base, for example 4-dimethylaminopyridine, followed by the addition of an acylating agent such as di-*tert*-butyldicarbonate. Hydroboration of the olefin with, for example, borane-tetrahydrofuran, followed by an oxidative work-up with, for example, basic hydrogen peroxide, affords the 4-hydroxytetrahydroquinoline, which may be oxidized with, for example, pyridinium chlorochromate, to afford a compound of structure **76A**. A compound of structure **76A** may then be deprotonated with a base, for example, sodium hydride, and treated with an alkylating agent such as iodomethane. Addition of an organomagnesium or organolithium reagent (R^5 = alkyl, aryl, etc.), or a reducing agent such as sodium borohydride (R^5 = hydrogen), affords an alcohol. Reduction of the alcohol with, for example, hydrogen over palladium on carbon, followed by deprotection of the nitrogen atom, affords a compound of structure **77A**. Nitration of a compound of structure **77A** by the action of nitric acid in the presence of, for example, sulfuric acid, followed by reduction of the nitro group with, for example, hydrogen over palladium on carbon, affords 7-amino-1,2,3,4-tetrahydroquinolines of structure **78A**. A Knorr cyclization with a β-keto ester effected by, for example, zinc chloride, affords a compound of structure **79A**. A compound of structure **79A** may be further transformed into a compound of structure **80A** by alkylation of the nitrogen atom, which can be accomplished in one of two ways. Treatment of a compound of structure **79A** with a base, such as sodium hydride, and an alkylating agent, such as benzyl bromide, affords a compound of structure **80A**. Alternatively, treatment of a compound of structure **79A** with an aldehyde, for example acetaldehyde or paraformaldehyde, in the presence of a reducing agent, for example sodium cyanoborohydride or sodium (triacetoxy)borohydride, affords a compound of structure **80A**.

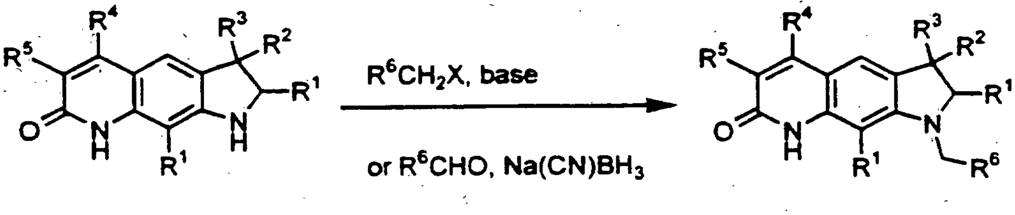
Scheme LIV



62A **81A**

The process of **Scheme LIV** involves the deprotonation of a compound of structure **62A** with, for example, sodium hydride, followed by treatment with an alkylating agent such as iodomethane to afford a compound of structure **81A**.

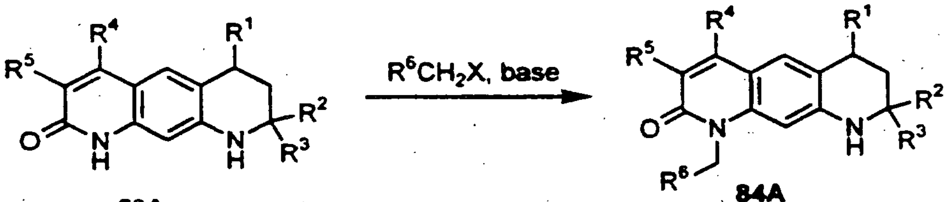
Scheme LV



82A **83A**

The process of Scheme LV involves the conversion of a compound of structure **82A** into a compound of structure **83A** by alkylation of the nitrogen atom, which can be accomplished in one of two ways. Treatment of a compound of structure **82A** with a base, such as sodium hydride, and an alkylating agent, such as benzyl bromide, affords a compound of structure **83A**. Alternatively, treatment of a compound of structure **82A** with an aldehyde, for example acetaldehyde or paraformaldehyde, in the presence of a reducing agent, for example sodium cyanoborohydride or sodium (triacetoxy)borohydride, affords a compound of structure **83A**.

Scheme LVI



53A **84A**

The process of **Scheme LVI** involves the deprotonation of a compound of structure **53A** with, for example, sodium hydride, followed by treatment with an alkylating agent such as iodomethane to afford a compound of structure **84A**.

It will be understood by those skilled in the art that certain modifications can be made to the above-described methods that remain within the scope of the present invention.

In a further aspect, the present invention provides several novel processes for the preparation of the compounds of the present invention. Each of these processes is illustrated in one or more of the Schemes shown above, and is described with particularity as follows.

Process 1 is depicted in **Scheme II** and begins with the conversion of a 4-bromoaniline (Compound **6**) to 6-bromo-1,2-dihydro-2,2,4-trimethylquinoline (Compound **7**) by treatment with acetone (0.01 M to 10 M) and 0.01-100 mol% of one or more catalysts (for example, *para*-toluenesulfonic acid, sulfuric acid, hydrochloric acid, boron trifluoride etherate, magnesium sulfate, or iodine) at -20°C to 300°C. Additives that inhibit polymerization (for example, 4-tert-butylcatechol) can also be used in addition to the catalyst(s). The aniline nitrogen is then protected. For example, protection as the *t*-butyl carbamate requires treatment of a solution (typical solvents include toluene, ether, THF) of Compound **7** with a strong base (for example, *n*-butyllithium, sodium hydride, potassium hydride) at -100°C to 100°C, followed by reaction with di-*t*-butyldicarbonate at -100°C to 100°C to afford the 6-substituted-1,2-dihydro N-1 protected quinoline (Compound **8**). The important steps of process 1 then begins when the halogen (e.g., bromine) of Compound **8** is replaced with either lithium by a lithium-halogen exchange reaction by treatment of a solution (typical solvents include toluene, ether, THF) of Compound **8** with an alkyllithium (for example, *t*-butyllithium, *n*-butyllithium) at -100°C to 100°C, or with a reactive metal(s), such as magnesium by treatment with magnesium metals (turnings or powder) or zinc, and either iodine or ethylene dibromide in an inert solvent (typical solvents include ether, THF, pentane) at -20°C to 200°C. The organolithium or organomagnesium intermediate is then allowed to react with a trialkylborate (for example, trimethylborate, triisopropylborate) at -100°C to 100°C. The organoborate intermediate is hydrolyzed with acid (for example, dilute aqueous hydrochloric acid or sulfuric acid) at -40°C to 100°C to afford the boronic acid (e.g., 6-boro-1,2-dihydro N-1 protected quinoline: Compound **9**). Alternatively, the organolithium or organomagnesium intermediate may be treated with an organotin species (for example, trimethyltin chloride, tributyltin chloride, etc.) at -100°C to 200°C to afford a trialkyltin quinolinoyl compound, a species useful in the coupling processes described in J.K.Stille et al., "4-Methoxy-4'-nitrobiphenyl", *Organic Syntheses* **1992**, *71*, 97, and T.N. Mitchell, "Palladium-Catalyzed Reactions of Organotin Compounds" *Synthesis* **1992**, 803, the disclosures of which are herein incorporated by reference. Treatment of a solution (typical solvents include toluene, DME, DMF) of Compound **9** with a coupling partner (an aryl, heteroaryl, or vinylbromide; an aryl, heteroaryl, or vinyliodide; or an aryl, heteroaryl, or vinyl triflate) in the presence of a catalytic amount of a palladium species [for example, tetrakis(triphenylphosphine)-palladium, allylpalladium chloride dimer, bis(triphenylphosphine)palladium dichloride], and aqueous base (for example, sodium carbonate, potassium carbonate) at -40°C to 200°C affords a 6-substituted-1,2-dihydro N-1 protected quinoline (structure **10**). Deprotection of a compound of structure **10**, for example, with acid (for example, trifluoroacetic acid) at -80°C to 200°C, affords the corresponding 6-substituted-1,2-dihydroquinoline (e.g., structure **4**).

Process 2 is depicted in **Scheme III** and involves the treatment of a solution (typical solvents include toluene, DME, DMF) of 6-halo-1,2-dihydro N-1 protected quinoline (Compound **8**) with an organoboron species (for example, phenylboronic acid, 3-nitrophenylboronic acid) or an organotin species [such as tributylphenyl tin or trimethyl(4-methoxyphenyl) tin] in the presence of a coupling partner and a catalytic amount of a palladium species [for example, tetrakis (triphenylphosphine)palladium, allylpalladium chloride dimer, bis(triphenylphosphine)palladium dichloride], and aqueous base (for example, sodium carbonate, potassium carbonate) at -40°C to 200°C to afford a 6-substituted-1,2-dihydro N-1 protected quinoline (structure **10**). Deprotection of a compound of structure **10** with acid (for example, trifluoroacetic acid) at -80°C to 200°C affords the 6-substituted-1,2-dihydroquinoline (structure **4**).

Process 3 is depicted in **Scheme XI** and involves the preparation of benzocoumarins from acyclic precursors. Thus, an ortho-bromoanisole (structure **36**) is lithiated with an alkyllithium (for example, *n*-butyllithium, *t*-butyllithium) at -100°C to 80°C in an inert solvent (typical solvents include toluene, ether, THF), and allowed to react with a trialkylborate (for example, trimethylborate, triisopropylborate) at -100°C to 100°C. Hydrolysis of the intermediate with acid (for example, dilute hydrochloric acid or sulfuric acid) at -40°C to 100°C, affords the corresponding 2-methoxyphenyl boronic acid (structure **37**). Alternatively, the organolithium or organomagnesium intermediate may be treated with a trialkyltin halide (for example, trimethyltin chloride, tributyltin chloride, etc.) at -100°C to 200°C to afford a trialkyltin aryl compound, a species useful in the coupling processes described above in **Process 1**. The important steps of process 3 begin with the palladium-catalyzed coupling of a 2-methoxyphenyl boronic acid (structure **37**) with a 2-halo-5-nitrobenzoic acid derivative (typical derivatives include the acid; any one of a number of esters, including methyl, ethyl, allyl, *t*-butyl, phenyl; or any one of a number of amides, including dimethyl, methyl, diallyl, allyl, dibenzyl) with a palladium catalyst (for example, tetrakis(triphenylphosphine) palladium, allylpalladium chloride dimer, bis(triphenylphosphine)palladium dichloride), and aqueous base (for example, sodium carbonate, potassium carbonate) at -40°C to 200°C affords the biaryl carboxylate (structure **39**). The product obtained from use of the acid as a coupling partner may be used directly; alternatively, deprotection by hydrolysis of the ester or the amide is accomplished with aqueous base (for example, potassium hydroxide or sodium hydroxide) or aqueous acid (for example, trifluoroacetic acid, hydrochloric acid, sulfuric acid) at -60°C to 300°C. The acid is converted to the acid chloride with, for example, thionyl chloride in an inert solvent (typical solvents include methylene dichloride, toluene, or 1,2-dichloroethane) at -80°C to 300°C. Intramolecular cyclization (acylation) is then effected by treatment of a solution of the acid chloride in an inert solvent (typical solvents include methylene dichloride, toluene, or 1,2-dichloroethane) with a Lewis acid (for example, aluminum trichloride, boron trifluoride) at -80°C to 300°C to yield the nitrobenzocoumarin. Reduction of the nitro group of the nitrobenzocoumarin with, for example, 1-200 atmospheres of hydrogen over a metal catalyst (for example, Pd/C, PtO_2), affords the desired aminobenzocoumarin (structure **40**). Treatment of compounds of structure **40** with acetone and a catalyst such as iodine affords the coumarino[3,4-*f*]quinoline (structure **41**), as described above in **Process 1**. The addition of an organometallic reagent, for example an organolithium or organomagnesium reagent, to a solution of a compound of structure **41** in an inert solvent at -100°C to 100°C affords an adduct. This adduct may be reduced by treatment of a solution of the adduct in an inert solvent (such as dichloromethane or toluene) with a strong protic or Lewis acid and a trialkylsilane, (for example, boron trifluoride or trifluoroacetic acid and triethylsilane or methyldiphenylsilane) at -80°C to 200°C, to afford a 5*H*-chromeno[3,4-*f*]quinoline (Compound of structure **42**).

Process 4 is depicted in **Scheme XIII** and involves the addition of an organometallic reagent, for example an organomagnesium or organolithium reagent, to a solution of a compound of structure **41** (i.e., a coumarino[3,4-*f*]quinoline) in an inert solvent (typical solvents include ether, THF, toluene) at -100°C to 100°C. Dehydration of the intermediate thus derived may be effect by treatment of a solution of the intermediate (typical solvents include in dichloromethane, ethanol, or toluene) with an acid (for example, *para*-

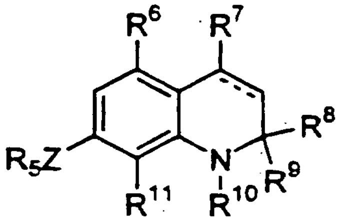
toluenesulphonic acid, methanesulphonic acid), to afford compounds of structure **45** (i.e., 5*H*-chromeno[3,4-*f*]quinolines).

Process 5 is depicted in **Scheme XVII** and begins with the acylation of a 3-nitroaryl, e.g., a 3-nitrophenol (structure **64**, Y=O), 3-nitroaniline (structure **64**, Y=NH), or 3-nitrothiophenol (structure **64**, Y=S), with an acylating agent (for example, di-*tert*-butyl dicarbonate or trimethylacetyl chloride), either with or without the addition of a base (for example, 4-dimethylaminopyridine, triethylamine, pyridine) in an inert solvent (typical solvents include dichloromethane, THF, toluene) at -100°C to 200°C, to afford the 5-protected 3-nitroaryl compound of structure **65**. Reduction of the nitro group with, for example, 1-200 atmospheres of hydrogen over a metal catalyst (for example, Pd/C, PtO_2), affords the corresponding 5-protected 3-aminoaryl (structure **66**). Treatment of a compound of structure **66** with acetone and a catalyst such as iodine and addition of a 1,2-dihydroquinoline affords the 5-protected 1,2-dihydroquinoline compound of structure **67**, as described above in **Process 1**. Deprotection, for example, by either acid (for example, hydrochloric acid, trifluoroacetic acid, sulfuric acid) or base (for example, sodium hydroxide) at -40°C to 300°C, followed by treatment of a solution (typical solvents include ethanol, toluene, methanol) of the corresponding aniline or phenol with a β-keto ester (structure **68**) in the presence of a Lewis acid (for example, zinc chloride, boron trifluoride, aluminum trichloride) at -40°C to 300°C, affords one or more of the four linear tricyclic 1,2-dihydroquinoline compounds (structures **57**, **69**, **70**, and **71**). A compound of structure **69** may be converted to a compound of structure **57** by treatment of a solution (typical solvents include toluene, dichloromethane) of a compound of structure **69** with an acid (for example, *para*-toluenesulphonic acid, hydrochloric acid) at -40°C to 300°C. In addition, a compound of structure **71** may be converted to a compound of structure **57** by treatment of a solution (typical solvents include toluene, dichloromethane) of a compound of structure **71** with, for example, *para*-chlorophenol.

Process 6 is a modification of **Process 5**. Thus, a solution (typical solvents include ether, THF, toluene) of a 3-aminoaryl, preferably 3-amino thioaryl, is treated with a strong base (for example, sodium hydride, *n*-butyllithium) at -100°C to 100°C, followed by the addition of an acylating agent (typical acylating agents include di-*t*-butyl dicarbonate, trimethylacetyl chloride, acetic anhydride) at -100°C to 200°C, to afford the corresponding the corresponding 5-protected 3-aminoaryl compound of structure **66** (Y=S). The conversion of a compound of structure **66** (Y=S) to the linear tricyclic 1,2-dihydroquinoline compounds of structures **57**, **69**, **70** and **71** (Y=S) is accomplished as described above in **Process 5**.

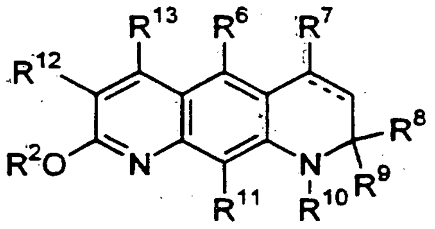
Process 7 is depicted in **Scheme XLVI**, and also is included as parts of **Schemes XLVIII, LII**, and **LIII**. **Process 7** begins with the nitration of a 1,2,3,4-tetrahydroquinoline (for example, a compound of structure **51A** in **Scheme XLVI**, or of structure **60A** in **Scheme XLVIII**, etc) with a nitrating agent. For example a mixture of sulfuric acid and nitric acid is added to a solution of the tetrahydroquinoline in sulfuric acid or sulfuric acid and a second, inert solvent such as nitromethane, at -80 °C to +40 °C. The nitro group of the resulting 7-nitro-1,2,3,4-tetrahydroquinoline is then reduced by hydrogenation over a metal catalyst (for example, Pd/C, PtO_2) under 1-200 atmosperes of hydrogen, to afford the corresponding aniline (a compound of structure **52A** in **Scheme XLVI** or of structure **72A** in **Scheme LII**, for example). Treatment of a solution (typical solvents include ethanol, toluene, methanol) of the aniline with a b-keto ester (structure **68**) in the presence of a Lewis acid (for example, zinc chloride, boron trifluoride, aluminum trichloride) at -40 °C to +300 °C, affords the desired quinoline, a compound of structure **53A** in **Scheme XLVI**, or of structure **73A** in **Scheme LII**, etc.

In yet another aspect, the present invention provides novel intermediates useful in the preparation of the steroid modulator compounds of the present invention. The intermediates of the present invention are defined as those having the formulae:



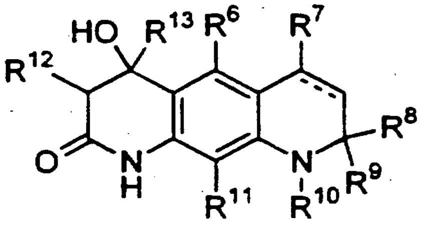
(I)

OR



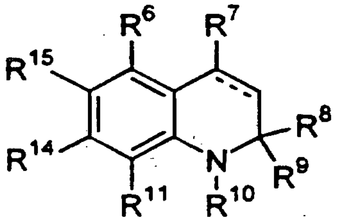
(II)

OR



(III)

OR



(IV)

wherein:

Z is O, S, or NR^1, where R^1 is hydrogen, $R^2C{=}O$, $R^2C{=}S$, $R^3OC{=}O$, $R^3SC{=}O$, $R^3OC{=}S$, $R^3SC{=}S$ or $R^3R^4NC{=}O$, where R^2 is hydrogen, a C_1 - C_6 alkyl or perfluoroalkyl, optionally substituted allyl or aryl methyl alkenyl, alkynyl, aryl or heteroaryl, and where R^3 and R^4 each independently are hydrogen, a C_1 - C_6 alkyl, optionally substituted allyl, arylmethyl, aryl or heteroaryl;

R^5 is hydrogen, $R^2C{=}O$, $R^2C{=}S$, $R^3OC{=}O$, $R^3SC{=}O$, $R^3OC{=}S$, $R^3SC{=}S$, or $R^3R^4NC{=}O$, where R^2, R^3 and R^4 have the same definitions as given above;

R^6 is hydrogen, a C_1 - C_6 alkyl, optionally substituted allyl, aryl methyl, alkenyl, alkynyl, aryl, heteroaryl, R^3O, $HOCH_2$, R^3OCH_2, F, Cl, Br, I, cyano, R^3R^4N or perfluoroalkyl, where R^3 and R^4 have the same definitions as given above;

R^7 through R^9 each independently are hydrogen, a C_1 - C_6 alkyl, allyl or optionally substituted allyl, arylmethyl, alkynyl, alkenyl, aryl, or heteroaryl, or
R^8 and R^9 taken together form a three- to seven-membered carbocylic or heterocyclic ring;

R^{10} is hydrogen, a C_1 - C_6 alkyl, optionally substituted allyl, arylmethyl, aryl, or heteroaryl, $R^2C=O$, $R^2C=S$, $R^3OC=O$, $R^3SC=O$, $R^3OC=S$, $R^3SC=S$ or $R^3R^4NC=O$, where R^2 through R^4 have the same definitions as given above;

R^{11} and R^{12} each independently represent hydrogen, a C_1 - C_6 alkyl, optionally substituted allyl, aryl methyl, alkenyl, alkynyl, aryl, heteroaryl, R^3O, $HOCH_2$, R^3OCH_2, F, Cl, Br, I, cyano, R^3R^4N or perfluoroalkyl, where R^3 and R^4 have the same definitions as given above;

R^{13} is hydrogen, a C_1 - C_6 alkyl, optionally substituted allyl, aryl methyl, alkenyl, alkynyl, aryl, heteroaryl, R^3O, $HOCH_2$, R^3OCH_2, R^3R^4N, CF_2Cl, CF_2OR^3 or perfluoroalkyl, where R^3 and R^4 have the same definitions as given above;

R^{14} is hydrogen, a C_1 - C_6 alkyl, optionally substituted allyl, aryl methyl, alkenyl, alkynyl, aryl, heteroaryl, R^3O, $HOCH_2$, R^3OCH_2, F, Cl, Br, I, cyano, R^3R^4N or perfluoroalkyl where R^3 and R^4 have the same definitions as given above; and

R^{15} is F, Cl, Br, I, $B(OR^{16})_2$, $SnR^{17}R^{18}R^{19}$ or OSO_2R^{20}, where R^{16} is hydrogen or a C_1 - C_6 alkyl, R^{17} through R^{19} each independently represent a C_1 - C_6 alkyl, R^2O or heteroaryl, R^{20} is a C_1 - C_6 alkyl, perfluoroalkyl, aryl, or heteroaryl, and R^2 has the same definition as given above.

Representative intermediate compounds useful in the preparation of the steroid modulator compounds of the present invention include: 1, 2-Dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 159); 9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 207); 8-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 208); 9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 209); 8-Ethoxy-1,2-dihydro-2,2,4-trimethyl-6-

trifluoromethyl-8-pyrido[5,6-g]quinoline (Compound 248); and 1,2,6,7-Tetrahydro-6-hydroxy-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 249).

The compounds of the present invention also includes racemate, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, any of the steroid modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and more preferably, in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired, e.g., intravenous, oral, topical, suppository or parenteral.

In preparing the compositions in oral liquid dosage forms (e.g., suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (e.g., powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent the most advantageous oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions such as Eucerin™ (Beiersdorf). Examples of suitable cream bases are Nivea™ Cream (Beiersdorf), cold cream (USP), Purpose Cream™ (Johnson & Johnson) hydrophilic ointment (USP), and Lubriderm™ (Warner-Lambert).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (e.g., tablet, capsule etc.) at from about 1 µg/kg of body weight to about 500 mg/kg of body weight, more preferably from about 10 µg/kg to about 250 mg/kg, and most preferably from about 20 µg/kg to about 100 mg/kg. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

The compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR, AR, ER, GR or MR in a cell background or extract. They are particularly useful due to their ability to selectively activate progesterone and androgen receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

Due to the selective specificity of the compounds of this invention for steroid receptors, these compounds can be used to purify samples of steroid receptors *in vitro*. Such purification can be carried out by mixing samples containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the receptors of choice, and then separating out the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation, and antibody complexing, among others.

The compounds and pharmaceutical compositions of the present invention can advantageously be used in the treatment of the diseases and conditions described herein. In this regard, the compounds and compositions of the present invention will prove particularly useful as modulators of human fertility, and in the treatment of female and male sex steroid-dependent diseases and conditions such as hormone replacement therapy, dysfunctional uterine bleeding, endometriosis, leiomyomas, acne, male-pattern baldness, osteoporosis, prostatic hyperplasia and various hormone-dependent cancers, such as cancers of the breast, ovaries, endometrium and prostate. The GR and MR active compounds and compositions of the present invention will also prove useful as affectors of carbohydrate, protein and lipid metabolism, electrolyte and water balance, as well as modulators of the functions of the cardiovascular, kidney, central nervous, immune, skeletal muscle and other organ and tissue systems.

The compounds and pharmaceutical compositions of the present invention possess a number of advantages over previously identified steroidal and non-steroidal compounds.

Furthermore, the compounds and pharmaceutical compositions of the present invention possess a number of advantages over previously identified steroid modulator compounds. For example, the compounds are extremely potent activators of PR and AR, preferably displaying 50% maximal activation of PR and/or AR at a concentration of less than 100 nM, more preferably at a concentration of less than 50 nM, more preferably yet at a concentration of less than 20 nM, and most preferably at a concentration of 10 nM or less. Also, the selective compounds of the present invention generally do not display undesired cross-reactivity with other steroid receptors, as is seen with the compound mifepristone (RU486; Roussel Uclaf), a known PR antagonist that displays an undesirable cross reactivity on GR and AR, thereby limiting its use in long-term, chronic administration. In addition, the compounds of the present invention, as small organic molecules, are easier to synthesize, provide greater stability and can be more easily administered in oral dosage forms than other known steroidal compounds.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-phenylquinoline (Compound **100**, structure **5** of **Scheme I**, where R^1=phenyl)

In a flame-dried round bottom (r.b.) flask equipped with a magnetic stir bar was dissolved 1,2-dihydro-2,2,4-trimethyl-6-phenylquinoline (15 mg, 60 µmol) and 10% Pd on C (10 mg) in anhydrous CH_2Cl_2 (3 mL). The flask was repeatedly evacuated and filled with N_2 to remove any residual O_2 and then H_2 gas was introduced. The solution was stirred at room temperature for 18 h, filtered though a Celite™ plug, and concentrated *in vacuo* to afford 7.8 mg (52 %) of Compound **100** as an off white solid. Data for Compound **100**: R_f = 0.71 (silica gel, hexane/EtOAc, 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.53 (d, *J* = 4.0, 1 H), 7.47 (m, 2 H), 7.35 (m, 2 H), 6.53 (d, *J* = 4.1, 1 H), 3.71 (bs, 1 H), 2.98 (m, 1 H), 1.79 (dd, *J* = 4.0, 8.0, 1 H), 1.41 (d, *J* = 4.0, 3 H), 1.23 (d, *J* = 8.0, 6 H)

EXAMPLE 2

1,2-Dihydro-2,2,4-trimethyl-6-(1,2,3-thiadiazol-5-yl)quinoline (Compound **101**, structure **4** of **Scheme I**, where R^1=2,3,4-thiadiazolyl)

To a dry 250-mL r.b. flask equipped with a magnetic stirring bar and a water cooled reflux condenser was added 4-(1,2,3-thiadiazolyl)aniline (0.990 g, 5.59 mmol) along with a catalytic amount of I_2 (≈50 mg) dissolved in acetone (HPLC grade, 70 mL). The resulting red solution was heated at reflux with constant stirring for 60 h. The reaction was followed by TLC (hexane/EtOAc, 3:1, visualized by short wave UV, the product appearing as a bright blue spot). After cooling to room temperature (rt), Celite™ (2.0 g) was added and the mixture was concentrated under reduced pressure to give a free flowing powder which was purified by silica gel chromatography (70 g silica gel 60, 240 mesh, hexane/EtOAc, 5:1) to afford 258 mg (18%) of Compound **101** as a light yellow solid: R_f= 0.35 (hexane/ ethyl acetate, 3:1). Data for Compound **101**: **^{1}H NMR** (400 MHz, C_6D_6): 7.86 (d, *J* = 2.0, 1 H), 7.70 (dd, *J* = 8.4, 2.1, 1 H), 7.34 (s, 1 H), 6.19 (d, *J* = 8.4, 1 H), 5.09 (s, 1 H), 3.29 (br s, 1 H), 1.87 (d, *J* = 1.2, 3 H), 1.02 (s, 6 H).

EXAMPLE 3

1,2-Dihydro-2,2,4-trimethyl-6-(1,3-oxazol-5-yl)quinoline (Compound **102**, structure **4** of **Scheme I**, where R^1=5-oxazolyl)

This compound was prepared using the procedure for EXAMPLE 2 from 4-(1,3-oxazol-5-yl)aniline (460 mg, 287 mmol) to afford Compound **102** (299 mg, 1.22 mmol, 43%) as a light brown solid: $R_f = 0.23$ (silica gel, hexane/EtOAc, 3:1). Data for Compound **102**: **^{1}H NMR** (400MHz, C_6D_6): 7.40 (d, J = 1.99, 1 H), 7.32 (s, 1 H), 7.26 (dd, J = 8.2, 2.0, 1 H), 7.14 (s, 1 H), 6.10 (d, J = 8.4, 1 H) , 5.06 (s, 1H), 3.23 (br s, 1 H), 1.79 (d, J = 1.2, 3 H), 1.00 (s, 6 H).

EXAMPLE 4

6-(4,5-Dichloroimidazol-1-yl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **103**, structure **4** of **Scheme I**, where R^1=4,5-dichloroimidazol-1-yl)

This compound was prepared using the procedure for EXAMPLE 2 from 4-(4,5-dichloroimidazol-1-yl)aniline (1.0 g, 44 mmol) to afford Compound **103** (234 mg, 17%) as an off-white solid: $R_f = 0.26$ (silica gel, hexane/ethyl acetate, 3:1). Data for Compound **103**: **^{1}H NMR** (400 MHz, C_6D_6) 7.12 (s, 1 H), 6.66 (d, J = 2.3, 1 H), 6.44 (dd, J = 8.4, 2.4, 1 H), 5.90 (d, J = 8.4, 1 H), 5.05 (s, 1 H), 3.20 (br s, 1 H), 1.66 (d, J = 1.4, 3 H), 0.99 (s, 6 H).

EXAMPLE 5

6-(4-Bromo-1-methylpyrazol-3-yl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **104**, structure **4** of **Scheme I**, where R^1=4-bromo-1-methylpyrazol-3-yl)

This compound was prepared using the procedure of EXAMPLE 2 from 4-(4-bromo-1-methylpyrazol-3-yl)aniline (1.0 g, 44 mmol) to afford Compound **104** (540 mg, 41%) as an off-white solid. Data for Compound **104**: $R_f = 0.23$ (silica gel, hexane/EtOAc, 3:1). **^{1}H NMR** (400 MHz, C_6D_6) 7.64 (s, 1 H), 7.01 (d, J = 1.8, 1 H), 6.90 (dd, J = 8.0, 1.8, 1 H), 6.10 (d, J = 7.9, 1 H), 5.04 (s, 1 H), 3.37 (s, 3 H), 3.23 (br s, 1 H), 1.75 (d, J = 1.2, 3 H), 0.99 (s, 6 H).

EXAMPLE 6

1,2-Dihydro-2,2,4-trimethyl-6-(3-pyridyl)quinoline (Compound **105**, structure 4 of **Scheme I**, where R^1=3-pyridyl)

3-(4-Nitrophenyl)pyridine (structure 2, where R^1=3-pyridyl): To a solution of H_2SO_4 (6 mL) cooled in an ice bath to 0°C was added 3-phenylpyridine (1.0 g, 6.4 mmol). The orange-red solution was vigorously stirred while HNO_3 (1 mL) was slowly added dropwise to give a cloudy light yellow solution. After stirring at room temperature for 20 min the solution was carefully poured into a beaker filled with ice (200 g). The solution was neutralized with 20% NaOH to give a cloudy white suspension which was extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried ($NaSO_4$) and concentrated *in vacuo* to give the desired product (1.2 g, 99%) as a light yellow solid. Data for 3-(4-nitrophenyl)pyridine: R_f = 0.47 (silica gel, methanol/$CHCl_3$, 5/95); **^{1}H NMR** (400 MHz, acetone-d_6) 8.99 (s, 1 H), 8.67 (s, 1 H), 8.37 (d, *J* = 7.0, 2 H), 8.18 (m, 1 H), 8.02 (d, *J* = 7.0, 2 H), 7.53 (m, 1 H).

3-(4-Aminophenyl)pyridine (structure 3, where R^1=3-pyridyl): In a flame-dried r.b. flask equipped with a magnetic stirring bar was dissolved 3-(4-nitrophenyl)pyridine (131 mg, 0.655 mmol) and 10% Pd on C (10 mg) in anhydrous CH_2Cl_2 (3 mL) was added. The flask was repeatedly evacuated and filled with N_2 to remove any residual O_2, and then H_2 gas was introduced. The solution was stirred at rt for 18 h, filtered though a Celite™ plug and concentrated *in vacuo* to give the desired amine (105 mg, 95%) as an off-white solid. Data for 3-(4-aminophenyl)pyridine: R_f = 0.17 (silica gel, methanol/$CHCl_3$, 5/95); **^{1}H NMR** (400 MHz, acetone-d_6) 8.77 (d, *J* = 2.3, 1 H), 8.42 (dd, *J* = 6.4, 1.6, 1 H), 7.88 (m, 1 H), 7.41 (d, *J* = 8.5, 2 H), 7.33 (m, 1 H), 6.78 (d, *J* = 8.5, 2 H), 4.86 (br s, 2 H).

1,2-Dihydro-2,2,4-trimethyl-6-(3-pyridyl)quinoline (Compound 105, structure 4, where R^1=3-pyridyl): This compound was prepared using the procedure of EXAMPLE 2 from 3-(4-aminophenyl)pyridine (105 mg, 0.62 mmol) to afford Compound **105** (0.5 mg, 0.3%) as an off-white solid. Data for Compound **105**: R_f = 0.44 (silica gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 9.13 (s, 1 H), 8.58 (d, *J* = 2.5, 1 H), 7.48 (m, 1 H), 7.36 (s, 1

H), 7.26 (s, 1 H), 6.96 (s, 1 H), 6.82 (m, 1 H), 6.26 (d, $J =$ 4.0, 1 H), 5.12 (s, 1 H), 1.80 (s, 3 H), 1.06 (s, 6 H).

EXAMPLE 7

6-(4-Fluorophenyl)-1,2,-dihydro-2,2,4-trimethylquinoline (Compound **106**, structure **4** of **Scheme II**, where R^1=4-fluorophenyl)

6-Bromo-1,2-dihydro-2,2,4-trimethylquinoline (Compound 7): A dry 500 mL r.b. flask equipped with a magnetic stir bar and a reflux condenser was charged with 4-bromoaniline (35.7g, 0.208 mol) and acetone (250 mL, Aldrich reagent grade). To this solution, I_2 (2.637 g, 0.05 equiv) was added turning the solution bright red. The mixture was heated to reflux with constant stirring for 4 days (approximately 90 hours). The reaction was monitored by TLC (20% ethyl acetate/methylene chloride; observed starting material and product under short wave UV). As judged by TLC, 50% of the starting material was consumed during the course of the reaction. The reaction mixture was cooled to room temperature and quenched with saturated $Na_2S_2O_3$ (200 mL). The aqueous mixture was partitioned into 2 phases using ethyl acetate (200 mL). The organic layer was rinsed with saturated $Na_2S_2O_3$ (3 x 75-100 mL) and brine (100 mL). The combined aqueous layers were extracted with ethyl acetate (100 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The crude dark material was purified by flash chromatography (800 mL silica, 50% ethyl acetate/methylene chloride) followed by recrystallization of isolated quinoline (hexane) yielding 8.22 g (15%) of Compound 7 (white crystals). Data for Compound 7: **^{1}H NMR** (400 MHz, acetone-d_6) 7.06 (d, $J =$ 2, 1H), 6.99 (dd, $J =$ 8, 2, 1H), 6.42 (d, $J =$ 8, 1H), 5.36 (s, 1H), 5.28 (br s, 1H) 1.92 (d, $J =$ 2, 3H), 1.24 (s, 6H).

6-Bromo-1-*tert*-butyloxycarbonyl-1,2-dihydro-2,2,4-trimethylquinoline (Compound **8**): An oven dried 250 mL r.b. flask equipped with a magnetic stirrer and a nitrogen inlet was charged with Compound 7 (4.04 g, 16.0 mmol). The white crystals were dissolved in 40 mL THF. The clear solution was cooled to -78°C with constant stirring. A thermocouple was used to monitor the reaction temperature. *n*-Butyllithium (11.2 mL, 16.8 mmol, 1.50 M) was added slowly by syringe over a period of 15 min (temperature maintained between -

70°C and -65°C) turning the reaction mixture bright yellow. The reaction was allowed to continue stirring at -75°C for an additional 15 min. The reaction was warmed to 0°C and the di-*tert*-butyl-dicarbonate (3.846 g, 17.62 mmol) was added in one portion. NOTE: a significant exotherm was observed with the addition of the dicarbonate from 0°C to 12°C. The reaction was monitored by TLC as it warmed to rt (50% ethyl acetate/methylene chloride) (3-5 hours). The reaction mixture was quenched with 1.0 M $Na_2S_2O_3$ (100 mL) and partitioned with ethyl acetate (100 mL). The organic layer was rinsed with 1.0 M $Na_2S_2O_3$ (2 x 50 mL) and brine (100 mL). The aqueous layers were combined and back extracted with methylene chloride (75 mL). The organic layers were combined and dried (Na_2SO_4). The crude mixture was purified by flash chromatography (400 mL silica, 2% ethyl acetate/hexane) to provide Compound **8** (3.765 g, 66.7%) as an oil. Data for Compound **8**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.30 ppm (s, 1H), 7.28 (d, *J* = 8, 1H), 7.11 (d, *J* = 8, 1H), 5.60 (s, 1H), 2.00 (s, 3H), 1.49 (s, 9H), 1.48 (s, 6H).

General Method 1: biaryl coupling of an aryl boronic acid with 6-Bromo-1,2-dihydro-2,2,4-trimethylquinoline (Compound 8): A 25 mL recovery flask equipped with a magnetic stir bar was charged with Compound **8** (1.0 equiv) in toluene (0.1 M). Tetrakis(triphenylphosphine)palladium (0.03 equiv), boronic acid ($R^1B(OH)_2$) (1.3 equiv, 0.1 M in ethanol) and potassium carbonate (2.0 equiv, 2.0 M) were added to the reaction flask sequentially under a nitrogen atmosphere. A reflux condenser was fitted to the flask and the cloudy reddish solution was stirred rapidly and heated to reflux for about 4 h until the starting material had been completely consumed as judged by TLC (15% ethyl acetate/hexane). The product mixture was then cooled to room temperature and quenched with saturated NH_4Cl (4-5 mL). Ethyl acetate (5 mL) was used to partition the mixture. The organic layer was rinsed with saturated NH_4Cl (2 x 5 mL). The aqueous layers were extracted with ethyl acetate (5 mL). The organic layers were combined, dried (Na_2SO_4), and purified as indicated.

6-(4-Fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **106**, structure **4**, where R^1=4-fluorophenyl): This compound was prepared according to General Method 1 from Compound **8** (119.3 mg, 0.472 mmol) and commercially available 4-fluorobenzeneboronic acid (84.1 mg, 0.601 mmol, Lancaster). The product, Compound **106** (5.0 mg, <1%), was isolated and purified by reverse phase HPLC (ODS, 80% methanol/water, 3.0 mL/min). Data for Compound **106**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.57 ppm (m, 2H), 7.27 (d, *J* = 2, 1H), 7.20 (dd, *J* = 12, 2, 1H), 7.13 (dd, *J* = 16, 8, 2H), 6.57 (d, *J* = 8, 1H), 5.38 (s, 1H), 5.26 (br s, 1H), 2.03 (d, *J* = 1.6, 3H), 1.28 (s, 6H).

EXAMPLE 8

1,2-Dihydro-6-(3-trifluoromethylphenyl)-2,2,4-trimethylquinoline (Compound **107**, structure **4** of **Scheme II**, where R^1=3-trifluoromethylphenyl)

This compound was prepared according to General Method 1 (EXAMPLE 7) from Compound **8** (100.0 mg, 0.396 mmol) and commercially available 3-trifluoromethylbenzeneboronic acid (97.8 mg, 0.515 mmol, Lancaster). Compound **107** (2.0 mg, <1%) was isolated and purified by reverse phase high pressure liquid chromatography (HPLC) (ODS, 80% methanol/water, 3.0 mL/min). Data for Compound **107**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.86 (d, *J* = 8, 1H), 7.85 (s, 1H), 7.60 (dd, *J* = 16, 8, 1H), 7.54 (d, *J* = 8, 1H), 7.38 (d, *J* = 2, 1H), 7.32 (dd, *J* = 8, 2, 1H), 6.61 (d, *J* = 8, 1H), 5.40 (s, 1H), 5.40 (s, 1H), 2.78 (s, 3H), 1.30 (s, 6H).

EXAMPLE 9

1,2-Dihydro-2,2,4-trimethyl-6-(4-nitrophenyl)quinoline (Compound **108**, structure **4** of **Scheme II**, R^1=4-nitrophenyl)

(1-*tert*-Butyloxycarbonyl-1,2-dihydro-2,2,4-trimethyl-6-quinolinyl)boronic acid (Compound **9**): A 25 mL r.b. flask, equipped with a magnetic stirring bar, was charged with Compound **8** (3.765 g, 10.67 mmol) under N_2. The oil was dissolved in 11 mL THF (anhydrous) and cooled to -78°C. *tert*-Butyllithium (12.6 mL, 21.4 mmol, 1.70 M) was added by syringe over a period of 10 min (maintaining temperature below -70°C) turning the reaction mixture from pale yellow to bright yellow. The reaction was allowed to continue at -75°C until all of the starting material had been consumed as judged by TLC (15% ethyl acetate/hexane).

Trimethyl borate (1.22 g, 1.33 mL, 11.7 mmol, 1.1 equiv) was added by syringe over 5-10 minutes (temperature between -70°C and -65°C). The reaction was monitored by TLC. Upon completion, the product mixture was quenched with saturated NH_4Cl (200 mL). Addition of ethyl acetate (200 mL) partitioned the mixture into 2 phases. The organic phase was washed with saturated NH_4Cl (100 mL) and brine (100 mL). The combined aqueous layers were extracted with ethyl acetate (100 mL). The organic layers were combined and dried (Na_2SO_4). The crude mixture was applied to a small column containing 200 mL silica and 15% ethyl acetate/hexane. The higher R_f impurities were eluted with 2 L of 10% ethyl acetate/hexane. The boronic acid, Compound **9**, was eluted with 500 mL ethyl acetate followed by 750 mL ethanol to provide 1.483 g (44%) of Compound **9**. Data for Compound **9**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.73 (d, J = 1.2, 1H), 7.66 (dd, J = 8, 1.2, 1H), 7.13 (d, J = 8, 1H), 5.49 (s, 1H), 2.01 (d, J = 1.6, 3H), 1.50 (s, 9H), 1.46 (s, 6H).

General Method 2: biaryl coupling of an arylbromide and (1-*tert*-butyloxycarbonyl-1,2-dihydro-2,2,4-trimethyl-6-quinolinyl)boronic acid (Compound 9): A 25 mL recovery flask equipped with a magnetic stirring bar, was charged with aryl bromide (1.0 equiv, 0.1 M in toluene). Tetrakis(triphenylphosphine)palladium (0.03-0.1 equiv), Compound **9** (1.0 equiv, 0.1 M in ethanol) and K_2CO_3 (2.0 equiv, 2.0 M) were added to the reaction flask sequentially under a nitrogen atmosphere. A reflux condenser was fitted to the flask and the cloudy reddish solution was stirred rapidly and heated to reflux for about 4 h until the starting material had been completely consumed as judged by TLC (15% ethyl acetate/hexane). The product mixture was then cooled to room temperature and quenched with saturated ammonium chloride (4-5 mL). Ethyl acetate (5 mL) was used to partition the mixture. The organic layer was rinsed with saturated ammonium chloride (2 x 5 mL). The aqueous layers were back extracted with ethyl acetate (5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. A solution of the crude product in dichloromethane (0.1-0.3 M) was cooled to -20°C (ice/acetone) and treated with trifluoroacetic acid (10-40 equiv). Stirring was continued for 5-15 min and the reaction mixture was treated with excess saturated $NaHCO_3$. The product was extracted with ethyl acetate (3 x). The extracts were washed with saturated $NaHCO_3$ (3 x), combined, dried (Na_2SO_4), concentrated, and purified as indicated.

1,2-Dihydro-2,2,4-trimethyl-6-(4-nitrophenyl)quinoline (Compound **108**, structure **4** of **Scheme II**, where R^1=4-nitrophenyl): This compound was prepared according to General Method 2 from Compound **9** (36.6 mg, 0.115 mmol) and commercially available bromonitrobenzene (19.4 mg, 0.96 mmol, Aldrich). Compound **108** was isolated and purified by recrystallization from hexane to afford 9.4 mg (38%) of Compound **108**. Data for Compound **108**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.23 (dd, *J* = 8, 1.6, 2H), 7.65 (dd, *J* = 8, 2, 2H), 7.33 (d, *J* = 2, 1H), 7.31 (dd, *J* = 8, 2.4, 1H), 6.51 (d, *J* = 8, 1H), 5.38 (s, 1H), 3.94 (br s, 1H), 2.06 (d, *J* = 1.2, 3H), 1.33 (s, 6H).

EXAMPLE 10

6-(2,3-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **109**, structure **4** of **Scheme II**, where R^1=2,3-dichlorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9). From Compound **9** (68.0 mg, 0.21 mmol) and commercially available 2,3-dichlorobromobenzene (40.1 mg, 0.18 mmol, Lancaster) was obtained a crude product which was isolated and purified by reverse phase HPLC (ODS column, 97% methanol/water, 3.0 mL/min) to afford 20 mg (29%) of Compound **109**. Data for Compound **109**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.39 (dd, *J* = 8, 1.6, 1H), 7.19 (dd, *J* = 16, 8, 1H), 7.23 (dd, *J* = 4, 1.6, 1H), 7.11 (d, *J* = 1.6, 1H), 7.05 (dd, *J* = 8, 1.6, 1H), 6.46 (d, *J* = 8, 1H), 5.34 (s, 1H), 3.82 (br s, 1H), 1.99 (s, 3H), 1.32 (s, 6H).

EXAMPLE 11

1,2-Dihydro-6-(2-hydroxycarbonyl-4-nitrophenyl)-2,2,4-trimethylquinoline (Compound **110**, structure **4** of **Scheme II**, where R^1=2-hydroxycarbonyl-4-nitrophenyl)

This compound was prepared according to the General Method 2 (EXAMPLE 9). From Compound **9** (68.0 mg, 0.21 mmol) and methyl 2-bromo-5-nitrobenzoate (446.6 mg, 1.72 mmol), 712 mg (92%) of the coupled quinolinylmethylester was obtained. A portion, 481 mg (1.06 mmol), of this intermediate was hydrolyzed using potassium hydroxide (149 mg, 2.6 mmol) in refluxing 4:1 methanol/water over a period of 3 h. The hydrolyzed product was isolated by extraction with ethyl acetate. The crude product was purified by SGC (200 mL silica, 30% ethyl acetate/hexane to 50% ethyl acetate/hexane) to afford 490 mg (guant) of N-*tert*-butyloxycarbonyl-1,2-dihydro-6-(2-hydroxycarbonyl-4-nitrophenyl)-2,2,4-trimethylquinoline. N-*tert*-butyloxycarbonyl-1,2-dihydro-6-(2-hydroxycarbonyl-4-nitrophenyl)-2,2,4-trimethylquinoline (49.0 mg, 0.11 mmol) was then treated with trifluoroacetic acid (0.34 mL, 4.5 mmol) to remove the *tert*-butyl carbonate group (1-5 minutes, 0°C). The quenched reaction mixture was purified by silica gel chromatography (SGC) (50 mL silica, 40% ethyl acetate/hexane) to afford 1.2 mg (<1%) of Compound **110**. Data for Compound **110**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.43 (d, *J* = 2.4, 1H), 8.33 (dd, *J* = 8, 2.4, 1H), 7.72 (d, *J* = 8, 1H), 7.08 (d, *J* = 2, 1H), 7.02 (dd, *J* = 8, 2, 1H), 6.57 (d, *J* = 8, 1H), 5.62 (br s, 1H), 5.41 (s, 1H), 1.96 (d, *J* = 2.4, 3H), 1.28 (s, 6H).

EXAMPLE 12

6-(3,4-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **111**, structure **4** of **Scheme II**, where R^1=3,4-dichlorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9). From Compound **9** (78.4 mg, 0.25 mmol) and commercially available 3,4-dichlorobromobenzene (56.7 mg, 0.25 mmol, Lancaster) was obtained a crude product which was isolated and purified by preparative thin layer chromatography (PTLC) (1000 µm, 10% ethyl acetate/hexane) to afford 22 mg (28%) of Compound **111**. Data for Compound **111**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.73 (s, 1H), 7.52 (d, *J* = 1.2, 2H), 7.32 (d, *J* = 2, 1H), 7.26 (dd, *J* = 8, 2, 1H), 6.57 (d, *J* = 8, 1H), 5.42 (br s, 1H), 5.37 (s, 1H), 2.03 (d, *J* = 1.2, 3H), 1.27 (s, 6H).

EXAMPLE 13

4-Ethyl-1,2-dihydro-2,2-dimethyl-6-phenylquinoline (Compound **112**, structure **13** of **Scheme II**, where R^1=phenyl, R^2=methyl)

N-tert-Butyloxycarbonyl-1,2-dihydro-2,2-dimethyl-4-hydroxymethyl-6-phenyl quinoline (structure **11**, where R^1=phenyl): A solution of *N-tert*-butyloxycarbonyl-1,2-dihydro-2,2,4-trimethyl-6-phenyl quinoline (structure **10**, where R^1=phenyl) (310 mg, 0.888 mmol) and selenium dioxide (345 mg, 3.11 mmol) in 17 mL of dioxane was heated to reflux for 3 h. The reaction mixture was quenched with 1:1 NaS_2O_3 (10%) / Na_2HCO_3 (10%), extracted with dichloromethane, dried ($MgSO_4$), and the organic phase was concentrated *in vacuo*. Purification by flash chromatography (silica gel, hexane/ethyl acetate, 4:1) gave 212 mg of the intermediate aldehyde along with 75 mg of the desired alcohol of structure **11,** where R^1=phenyl. The aldehyde was treated with sodium borohydride in 25 mL of methanol at 0°C. After 1 h at 0°C, the reaction mixture was quenched with water, extracted with ethyl acetate and concentrated *in vacuo* to give an oil that was purified by flash chromatography (silica gel, hexane/ethyl acetate, 4:1) providing structure **11,** where R^1=phenyl (240 mg, 84%). **^{1}H NMR** (acetone d_6) 7.68 (d, *J* = 9, 2H), 7.61 (d, *J* = 1.8, 1H), 7.47 (dd, *J* = 6.2, 1.8, 1H), 7.41 (d, *J* = 6.4, 2H), 7.29 (m,2H), 5.80 (s, 1H), 4.51 (d, *J* = 6.8, 2H), 4.12 (t, *J* = 6.8,1H), 1.52 (br s, 15H).

N-tert-Butyloxycarbonyl-4-bromomethyl-1,2-dihydro-2,2-dimethyl-6-phenyl quinoline (structure **12**, where R^1=phenyl): To a solution of *N-tert*-butyloxycarbonyl-1,2-dihydro-2,2-dimethyl-4-hydroxymethyl-6-phenylquinoline (structure **11**, where R^1 = phenyl) (230 mg, 0.630 mmol) and carbon tetrabromide (220 mg, 0.662 mmol) in 5 mL of dichloromethane at 0°C was added triphenylphosphine (174 mg, 0.662 mmol) in 2 mL of dichloromethane. The reaction mixture was allowed to warm to rt and stirred for 1 h. The mixture was concentrated *in vacuo* to a residue that was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 9:1) to give structure **12**, where R^1=phenyl (72 mg, 27%). **^{1}H NMR** (acetone d_6) 7.67 (m, 3H), 7.52 (dd, *J* = 8.7, 2.1, 1H), 7.45 (t, 2H), 7.32 (m, 2H), 6.07 (s, 1H), 4.60 (s, 2H), 1.55 (s, 6H), 1.53 (s, 9H).

4-Ethyl-1,2-dihydro-2,2-dimethyl-6-phenylquinoline (Compound **112**, structure **13** of **Scheme II**, where R^1=phenyl, R^2=methyl): To a solution of *N-tert*-butyloxycarbonyl-4-bromomethyl-1,2-dihydro-2,2-dimethyl-6-phenylquinoline (structure **12**, where R^1=phenyl) (20 mg, 0.047 mmol) and copper (I) iodide (4 mg, 0.02 mmol) in 1 mL of anhydrous ether at 0°C was added MeMgBr (0.060 mL, 3 M in ether). After 30 min of stirring at 0°C, the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to provide an oil which was purified by SGC (silica gel, hexane/ethyl acetate, 9:1) giving *N-tert*-butyloxycarbonyl-4-ethyl-1,2-dihydro-2,2-dimethyl-6-phenylquinoline (16 mg, 91%). **^{1}H NMR** (acetone-d_6) 7.65 (d, J = 8.7, 2H), 7.51 (dd, J = 8.0, 1.7, 1H), 7.29 (m, 2H), 7.43 (m, 3H), 5.56 (s, 1H), 2.55 (q, J = 8.9, 2H), 1.51 (s, 6H), 1.57 (s, 9H), 1.19 (t, J = 8.9, 3H). To a solution of *N-tert*-butyloxycarbonyl-4-ethyl-1,2-dihydro-2,2-dimethyl-6-phenylquinoline (16 mg, 0.044 mmol) in 1 mL of dichloromethane at 0°C was added 0.3 mL of trifluoroacetic acid. After 10 min of stirring, the reaction was quenched with saturated $NaHCO_3$, and extracted with dichloromethane. The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to provide an oil that was purified by SGC (silica gel, hexane/ethyl acetate, 7:3) to provide 3 mg (25%) of Compound **112**. Data for Compound **112**: **^{1}H NMR** (acetone-d_6) 7.55 (d, J = 8.6, 2H), 7.37 (m, 3H), 7.23 (m, 2H), 6.59 (d, J = 8.26, 1H), 5.38 (s,1H), 3.76 (s, 1H), 2.48 (q, J = 7.4, 2H), 1.29 (s, 6H), 1.17 (t, J = 7.4, 3H).

EXAMPLE 14

1,2-Dihydro-2,2-dimethyl-6-phenyl-4-propylquinoline (Compound **113**, structure **13** of Scheme II, where R^1=phenyl, R^2=ethyl)

To a solution of *N-tert*-butyloxycarbonyl-4-bromomethyl-1,2-dihydro-2,2-dimethyl-6-phenyl quinoline (structure **12**, where R^1=phenyl) (20 mg, 0.047 mmol) and copper (I) iodide (4 mg, 0.019 mmol) in 1 mL of anhydrous ether at 0°C was added EtMgBr (0.06 mL, 3M in ether). After 30 min of stirring at 0°C, the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo* to provide an oil that was used directly in the next step. To the crude quinoline (20 mg, 0.053 mmol) in 1 mL of dichloromethane at 0°C was added 0.3 mL of trifluoroacetic acid. After 10 min of stirring, the reaction was quenched with aqueous saturated solution of $NaHCO_3$ and extracted with dichloromethane. The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to provide an oil that was chromatographed (silica gel, hexane/ethyl acetate, 7:3) to give Compound **113** (9 mg, 61%). Data for Compound **113**: **^{1}H NMR** (acetone-d_6) 7.53 (m, 2H), 7.40 (m, 3H), 7.24 (m, 2H), 6.58 (d, *J* = 8.14, 1H), 5.38 (s, 1H), 3.76 (s, 1H), 2.45 (t, *J* = 7.40, 2H), 1.60 (sx, *J* = 7.39, 2H), 1.29 (s, 6H), 0.99 (t, *J* = 7.27, 3H).

EXAMPLE 15

6-(2-Chlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **114**, structure **4** of **Scheme II**, where R^1=2-chlorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9). From Compound **9** (48.5 mg, 0.15 mmol) and commercially available 2-chlorobromobenzene (17.8 mL, 0.15 mmol, Lancaster) 15 mg (34%) of Compound **114** was isolated. Data for Compound **114**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.45 (dd, *J* = 8, 1.2, 1H), 7.36 (dd, *J* = 8, 2, 1H), 7.33 (ddd, *J* = 16, 8, 1.2, 1H), 7.23 (ddd, *J* = 16, 8, 2, 1H), 7.11 (d, *J* = 2, 1 H), 7.03 (dd, *J* = 8, 2, 1H), 6.53 (d, *J* = 8, 1H), 5.35 (s, 1H), 5.31 (br s, 1H), 1.97 (d, *J* = 1.6, 3H), 1.28 (s, 6H).

EXAMPLE 16

1,2-Dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound **116**, structure **17** of **Scheme IV**, where R^{1-6}=H, X=CH_2)

General Method 3: 1,2-dihydroquinoline formation from an aniline: To a dry 500-mL r.b. flask equipped with a magnetic stirring bar and a water cooled reflux condenser was added structure **15** along with I_2 (0.05-0.2 equiv) dissolved in acetone (0.1-0.5 M). The resulting red solution was heated at reflux with constant stirring for 60 h. The reaction was followed by TLC (hexane/EtOAc, 3:1, visualized by short wave UV, the product appearing as a bright blue spot). After cooling to room temperature, Celite™ (2.0 g) was added and the mixture was concentrated under reduced pressure to give a free flowing powder which was purified by flash column chromatography (70 g silica gel 60, 240 mesh, hexane/EtOAc, 5:1) to afford a mixture of isomers of structures **16** and **17**.

1,2-Dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound **116**, structure **17** of **Scheme IV**, where R^{1-6}=H, X=CH_2): This compound was prepared according to General Method 3 from structure **15** (where R^{1-6}=H, X=CH_2) (5.0 g, 27 mmol) to afford a mixture of

Compound **115** (structure **16** of **Scheme IV**, where R^{1-6}=H, X=CH_2)(1.64 g, 22.7%) and Compound **116** (336 mg, 4.65 %) in an 85:15 ratio (as determined by ^{1}H NMR). Data for Compound **116:** R_f= 0.57 (silica gel, hexane/EtOAc, 3:1). **^{1}H NMR** (400 MHz, C_6D_6) 7.62 (d, *J* = 8.0, 1H), 7.45 (d, *J* = 8.0, 1H), 7.28 (d, *J* = 7.3, 1 H), 6,31 (d, *J* = 8.0, 1H), 5.19 (s, 1 H), 3.74 (s, 2 H), 3.28 (br s, 1 H), 1.98 (d, *J* = 1.2, 3 H), 1.08 (s, 6 H).

EXAMPLE 17

8-Bromo-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **117**, structure **16** of **Scheme IV**, where R^{2-4}, R^6=H, R^5=Br, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from structure **15** (where R^{1-4}, R^6=H, R^5=Br, X=CH_2) (2.0 g, 7.7 mmol) to afford 376 mg (49%) of Compound **117** as a rose colored solid (along with Compound **127, Example** 18). Data for Compound **117**: R_f= 0.53 (silica gel, hexane/EtOAc, 3:1). **^{1}H NMR** (400 MHz, C_6D_6) 7.38 (m, 3H), 6.17 (s, 1H), 5.15 (s, 1 H), 3.34 (s, 2 H), 3.27 (br s, 1 H), 1.93 (d, *J* = 1.0, 3 H), 1.08 (s, 6 H).

EXAMPLE 18

7-Bromo-1,2-dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound **127**, structure **17** of **Scheme IV**, where R^{1-4}, R^6=H, R^5=Br, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from structure **15** (where R^{1-4}, R^6=H, R^5=Br, X=CH_2) (2.0 g, 7.7 mmol) to afford a mixture of Compounds **117** and **127**. Purification by silica gel chromatography afforded pure **117** (376 mg, 49%) (EXAMPLE 17) and mixed fractions containing **117** and **127**. Compound **127** was purified by reverse phase HPLC (ODS column, 95% methanol/water, 3.0 mL/min). Data for Compound **127:** R_f= 0.53 (silica gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, C_6D_6) 7.38 (d, *J* = 8.3, 1 H), 7.31 (s, 1 H), 7.29 (d, *J* = 8.0, 1 H), 7.19 (d, *J* = 8.0, 1 H), 6.25 (d, *J* = 8.1, 1 H), 5.16 (s, 1 H), 3.52 (s, 2 H), 3.32 (br s, 1 H), 1.91 (d, *J* = 1.4, 3 H), 1.05 (s, 6 H).

EXAMPLE 19

1,2-Dihydro-2,2,4-trimethylbenzo[b]furano[3,2-*g*]quinoline (Compound **118**, structure **16** of **Scheme IV**, where R^{2-6}=H, X=O)

This compound was prepared according to General Method 3 (EXAMPLE 16) from structure **15** (where R^{1-6}=H, X=O) (1.0 g, 5.5 mmol) to afford Compound **118** (264 mg, 18.4%) as a yellow solid, and Compound **119** (936 mg, 65%) as a clear colorless oil. Data for Compound **118:** R_f = 0.44 (hexane/EtOAc, 3:1); ^{1}**H NMR** (400MHz, C_6D_6) 7.61 (d, *J* = 6.9, 1H), 7.56 (s, 1 H), 7.41 (d, *J* = 8.0, 1H), 7.13 (m, 2 H), 6.38 (s, 1 H), 5.12 (s, 1 H), 3.28 (br s, 1 H), 1.91 (s, 3 H), 1.05 (s, 6 H).

EXAMPLE 20

1,2-Dihydro-2,2,4-trimethylbenzo[b]furano[2,3-*f*]quinoline (Compound **119**, structure **17** of **Scheme IV**, where R^{1-6}=H, X=O)

This compound was prepared according to General Method 3 (EXAMPLE 16) from structure **15** (where R^{1-6}=H, X=O) to afford Compound **118** (264 mg, 1.00 mmol, 18.4%) as a yellow solid and Compound **119** (936 mg, 3.55 mmol, 65.1%) as a clear colorless oil. Data for Compound **119**: R_f= 0.44 (silca gel, hexane/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, C_6D_6) 7.63 (dd, *J* = 7.4, 1.5, 1 H), 7.41 (d, *J* = 8.2, 1 H), 7.35 (d, *J* = 7.3, 1 H), 7.11 (m, 2 H), 6.19 (d, *J* = 8.4, 1 H), 5.11 (s, 1 H), 3.38 (br s, 1 H), 2.49 (d, *J* = 1.2, 3 H), 1.06 (s, 6 H).

EXAMPLE 21

6-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound **120**, structure **17** of **Scheme IV**, where R^{1-5}=H, R^6=F, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from structure **15** (where R^{1-5}=H, R^6=F, X=CH_2) (1.0 g, 5.0 mmol) to afford 248 mg (18%) of a mixture of Compounds **120** and **121**. Pure samples of Compounds **120** and **121** were obtained by preparative thin layer chromatography (PTLC) (1000 μm, hexane/EtOAc, 9:1). Data for Compound **120**: R_f = 0.70 (hexane/ EtOAc 3:1); ^{1}**H NMR** (400 MHz, C_6D_6) 7.38 (d, *J* = 8.0, 1 H), 7.29 (d, *J* = 7.5, 1 H), 7.09 (dd, *J* = 8.1, 5.3, 1 H), 6.8 (dd, *J* = 8.6, 8.6, 1 H), 6.26 (d, *J* = 8.0, 1 H), 5.13 (s, 1 H), 3.81 (s, 2 H), 3.32 (br s, 1 H), 1.88 (d, *J* = 1.2, 3 H) 1.05 (s, 6 H).

EXAMPLE 22

9-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **121**, structure **16** of **Scheme IV**, where R^{2-5}=H, R^6=F, X=CH_2)

This compound was obtained as described above for Compound **120** (EXAMPLE 21). Data for Compound **121**: R_f = 0.71 (silica gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, C_6D_6) 7.48 (s, 1 H), 7.25 (d, *J* = 7.4, 1 H), 7.07 (dd, *J* = 7.8, 5.4, 1 H), 6.80 (dd, *J* = 8.7, 8.7, 1 H), 6.13 (s, 1 H), 5.15 (s, 1 H), 3.63 (s, 2 H), 3.28, (br s, 1H), 1.93 (d, *J* = 1.2, 3 H) 1.09 (s, 6 H).

EXAMPLE 23

1,2-Dihydro-9-hydroxymethyl-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **122**, **Scheme V**).

Methyl 1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline-9-carboxylate (structure **16** of **Scheme IV** where R^{2-5}=H, R^6=CO_2CH_3, X=CH_2): This compound was prepared according to General Procedure 1 from methyl 2-aminofluoreno-8-carboxylate to afford 872 mg (65%) of methyl 1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline-8-carboxylate (structure **16** of **Scheme IV** where R^{2-5}=H, R^6=CO_2CH_3, X=CH_2) as an off white solid. Data for methyl 1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline-9-carboxylate: **^{1}H NMR** (400 mHz, C_6D_6) 8.03 (d, *J* = 7.8, 1 H), 7.56 (d, *J* = 7.4, 1 H,), 7.50 (s, 1 H,), 7.20 (dd, *J* = 15, 7.5, 1 H), 6.32 (s, 1 H), 5.17 (s, 1 H), 4.28 (s, 2H), 3.55 (s, 3H), 1.97 (d, *J* = 1.3, 3 H), 1.10 (s, 6H).

1,2-Dihydro-9-hydroxylmethyl-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **122**, **Scheme V**): In a r.b. flask equipped with a magnetic stirring bar was dissolved methyl 1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline-9-carboxylate (23 mg, 72.1 μmol) in 10 mL dry THF. The solution was stirred at -78°C for 10 min and DIBAl-H (1.0 M in hexanes; 0.43 mL, 6 equiv) was slowly added. After stirring for 20 min the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ (100 mg) and the solution was warmed to rt, at which time the reaction mixture became a white gelatinous suspension. The suspension was filtered and washed repeatedly with EtOAc. The washings and filtrate were combined and concentrated *in vacuo* to give 10 mg (49%) of Compound **122** as a white solid. Data for Compound **122**: R_f = 0.23 (silica gel, hexane/EtOAc, 3:1). ^{1}**H NMR** (400 MHz, acetone-d_6) 7.55 (d, *J* = 7.4, 1H), 7.50 (s, 1H); 7.26 (dd, *J* = 15, 7.5, 1H); 7.18 (d, *J* = 7.4, 1H); 6.73 (s, 1H); 5.36 (s, 1H); 5.21 (s, 1H); 4.72 (d, *J* = 5.8, 2H); 4.06 (dd, *J* = 11.4, 5.7, 1H); 3.20 (s, 2H); 2.78 (s, 3H); 1.28 (s, 6H).

EXAMPLE 24

8-Chloro-1,2-dihydro-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **123**, structure **16**, **Scheme IV**, where R^{2-4},R^6=H, R^5=Cl, X=CH_2)

2-Amino-7-chlorofluorene (structure **15**, **Scheme IV**, where R^{1-4},R^6=H, R^5=Cl, X=CH_2): A 100 mL round-bottom flask was charged with structure **14** (where, R^{2-4},R^6=H, R^5=Cl, X=CH_2) (496 mg, 2.02 mmol) and methylene chloride (20 mL) and 10% Pd/C (0.5g) was added to the solution. The reaction vessel was flushed with nitrogen and stirred under an atmosphere of hydrogen overnight (~15 hours), at which time the starting material was completely consumed as judged by TLC (50% ethyl acetate/hexane). The flask was flushed with nitrogen before exposing the mixture to air. The product mixture was diluted with ethyl acetate (50 mL) and washed with brine (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The crude product, structure **15** (where R^{1-4},R^6=H, R^5=Cl, X=CH_2)(400 mg, 92%), was used in the next step without purification.

8-Chloro-1,2-dihydro-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **123**, structure **16**, **Scheme IV**, where R^{2-4},R^6=H, R^5=Cl, X=CH_2): This compound was prepared according to General Method 3 (EXAMPLE 16) from structure **15** (where R^{1-4},R^6=H, R^5=Cl, X=CH_2)(400 mg, 1.85 mmol) and acetone (60 mL, Aldrich reagent grade) to afford Compound **123** and structure **17**, where R^{2-4},R^6=H, R^5=Cl, X=CH_2. Purification by PTLC (reverse phase, 80% methanol/water) provided 1.8 mg (<1%) of Compound **123**. Data for Compound **123**: ^{1}**H NMR:** (400 MHz, acetone-d_6) 7.59 (d, *J* = 8, 1H), 7.46 (s, 1H), 7.39 (d, *J* = 2, 1H), 7.24 (dd, *J* = 8, 2, 1H), 6.67 (s, 1H), 5.35 (s, 1H), 5.26 (br s, 1H), 3.71 (s, 2H), 1.98 (s, 3H), 1.24 (s, 6H).

EXAMPLE 25

8-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-g]quinoline (Compound 124, structure 16, Scheme IV, where R^{2-4},R^6=H, R^5=F, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-7-fluorofluorene (structure 15, where R^{1-4},R^6=H, R^5=F, X=CH_2) (100 mg, 500 µmol) to afford 43 mg (31%) of a mixture of Compound **124** and structure **17**, where R^{1-4},R^6=H, R^5=F, X=CH_2, in a 9:1 ratio. A small aliquot of this mixture was dissolved in acetone and purified by reverse phase preparative TLC (C-18, 20 x 20 cm, 1000 µm, MeOH / H_2O, 5:1) to give Compound **124** as a brown solid. Data for Compound **124:** R_f = 0.59 (silca gel, hexane/EtOAc, 3:1). **^{1}H NMR** (400 MHz, C_6D_6) 7.43 (s, 1 H), 7.24 (m, 1 H), 6.96 (m, 2 H), 6.21 (s, 1 H), 5.18 (s, 1 H), 3.38 (s, 2 H), 1.96 (s, 3 H), 1.11 (s, 6 H).

EXAMPLE 26

8-Acetyl-1,2-dihydro-2,2,4-trimethylindeno[1,2-g]quinoline (Compound 125, structure 16, Scheme IV, where R^{2-4},R^6=H, R^5=$COCH_3$, X=CH_2)

In a r.b. flask equipped with a magnetic stir bar was dissolved Compound **115** (EXAMPLE 16) (54 mg, 0.021 mmol) in CH_2Cl_2 (3 mL). To this solution was added freshly distilled acetyl chloride (20 µL, 1.3 equiv). The reaction mixture was stirred for 10 min, and $AlCl_3$ (≈30 mg) was added. The reaction was followed by TLC (hexane/EtOAc, 3:1, visualized by short wave UV). After 30 min, the black solution was quenched with H_2O (10 mL), stirred for 2 h, then extracted with EtOAc (2 x 20 mL), washed with brine (2 x 20 mL), dried (Na_2SO_4), and concentrated on Celite™. Purification by flash column chromotography (20 g silica gel 60, 240 mesh, hexane/EtOAc, 5:1) provided 3.7 mg (6%) of Compound **125** as a light yellow solid. Data for Compound **125**: R_f = 0.59 (silca gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, C_6D_6) 8.06 (s, 1 H), 7.94 (d, J = 8.0, 1 H), 7.53 (s, 1 H), 7.46 (d, J = 8.0, 1 H), 6.22 (s, 1 H), 5.16 (s, 1 H), 3.50 (s, 2 H), 2.28 (s, 3 H), 1.94 (d, J = 1.4, 3H), 1.10 (s, 6 H).

EXAMPLE 27

6-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **126**, structure **16**, **Scheme IV**, where R^2,R^{4-6}=H, R^3=F, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-5-fluorofluorene (structure **15**, where R^2,R^{4-6}=H, R^3=F, X=CH_2) (360 mg, 1.72 mmol) to afford 125 mg (26%) of Compound **126** as a light brown solid. Data for Compound **126**: R_f = 0.63 (silca gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, acetone-d_6): 7.55 (s, 1 H), 7.25 (d, *J* = 7.3, 1 H), 7.12 (m, 1 H), 7.02 (d, *J* = 10, 10, 1 H) 6.73 (s, 1 H), 5.39 (s, 1H), 3.81 (s, 2 H) 2.87 (s, 3 H), 1.28 (s, 6 H).

EXAMPLE 28

1,2-Dihydro-2,2,4-trimethyl-7-nitroindeno[2,1-*f*]quinoline (Compound **128**, structure **17**, **Scheme IV**, where R^{1-4},R^6=H, R^5=NO_2, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-7-nitrofluorene (100 mg, 0.44 mmol) to afford 2 mg (2%) of Compound **128** as a red solid. Data for Compound **128**: R_f = 0.46 (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 8.25 (s, 1 H), 8.19 (d, *J* = 7.8, 1 H), 7.80 (d, *J* = 7.7, 1 H), 7.65 (s, 1 H), 6.77 (s, 1 H), 5.70 (br s, 1 H), 5.45 (s, 1 H), 3.88 (s, 2 H), 2.10 (s, 3 H), 1.31 (s, 6 H).

EXAMPLE 29

1,2-Dihydro-2,2,4-trimethyl-8-nitroindeno[1,2-*g*]quinoline (Compound **129**, structure **16**, **Scheme IV**, where R^{2-4},R^6=H, R^5=NO_2, X=CH_2)

This compound was prepared according to General Method 1 from 2-amino-7-nitrofluorene (100 mg, 0.44 mmol) to afford 1.0 mg (<1%) of Compound **129** as a red solid. Data for Compound **129**: R_f = 0.46 (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 8.30 (s, 1 H), 8.19 (d, *J* = 8.0, 1 H), 7.78 (d, *J* = 7.7, 1 H), 7.59 (d, *J* = 7.8, 1 H), 6.70 (d, *J* = 7.8, 1 H), 5.70 (br s, 1 H), 5.43 (s, 1 H), 4.26 (s, 2 H), 2.30 (s, 3 H), 1.31 (s, 6 H).

EXAMPLE 30

6,9-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **130**, structure **16**, **Scheme IV**, where R^2,R^{4-5}=H, R^3,R^6=F, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-5,8-difluorofluorene (structure **15**, where R^2,R^{4-5}=H, R^3,R^6=F, X=CH_2) (460 mg, 2.03 mmol) to afford 94 mg (15%) of Compound **130** as a light brown solid. Data for Compound **130**: R_f = 0.56 (silica gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, C_6D_6) 7.92 (s, 1 H), 6.68 (ddd, *J* = 9.1, 6.3, 3.6, 1 H), 6.49 (ddd, *J* = 8.5, 6.0, 3.5, 1 H), 6.07 (s, 1 H), 5.09 (s, 1 H), 3.55 (s, 2 H), 1.88 (d, *J* = 1.1, 1 H), 1.06 (s, 6 H).

EXAMPLE 31

7-Fluoro-1,2-dihydro-2,2,4-trimethyl-11-(thiomethyl)indeno[2,1-*f*]quinoline (Compound **131**, structure **17** of **Scheme IV**, where, R^1=SCH_3, R^{2-4}, R^6=H, R^5=F, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-7-fluoro-3-methylthiofluorene (structure **15**, where R^1=SCH_3, R^{2-4}, R^6=H, R^5=F) (250 mg, 1.17 mmol) to afford 29 mg (7.5%) of Compound **131** (28.6 mg, 81 μmol, 7.5%) as a white solid. Data for compound **131**: R_f = 0.55 (silica gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 mHz, C_6D_6) 7.78 (s, 1 H), 7.19 (m, 1 H), 6.90 (s, 1 H,), 6.88 (s, 1H), 5.44 (s, 1 H), 5.22 (s, 1 H), 3.54 (s, 2H), 2.05 (s, 3H), 1.92 (d, *J* = 1.2, 3 H), 1.68 (s, 6 H).

EXAMPLE 32

5,8-Difluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **132**, **Scheme VII**).

3,2'-Difluoro-2-biphenic acid (Compound **23**, **Scheme VII**): A flame-dried 50 mL r.b. flask fitted with an air-cooled condenser containing methyl 2-bromo-5-fluorobenzoate (Compound **21**, **Scheme VII**) (4.00 g, 17.16 mmol) and 2-iodofluorobenzene (Compound **22**, **Scheme VII**) (19.05 g, 85.82 mmol, 5.00 equiv) was heated to 176°C, at which time unactivated copper powder (15.0 g, 236 mmol, 13.8 equiv) was added portion-wise over 40 min as the temperature was gradually raised to 190°C. After an additional 40 min at 190°C, the mixture was allowed to cool to rt and was filtered through a bed of Celite™ on a fritted-glass funnel, rinsing with 250 mL ethyl acetate. Concentration under reduced pressure afforded an oil which was shown by ^{1}H NMR to be composed of the desired Ullmann hetero-coupling product, along with some 2,2'-difluorobiphenyl, and a small amount of uncoupled methyl 2-bromo-5-fluorobenzoate. This crude product mixture was then dissolved in 60 mL THF, and the ester was hydrolyzed by treatment with a large excess of 10% aqueous NaOH at reflux. After 24 h, thin layer chromatography (TLC) analysis indicated complete consumption of starting material, and the crude reaction mixture was neutralized to pH 4 with 1 N aqueous HCl. The reaction mixture was then extracted with ethyl acetate (150 mL), and the organic phase was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel chromatography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 2.64 g (62%) of Compound **23** as a colorless, oily solid. Data for **23**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.76 (dd, *J* = 9.1, 2.2, 1H), 7.32 (m, 3H), 7.26 (ddd, *J* = 9.5, 7.8, 1.8, 1H), 7.18 (ddd, *J* = 8.1, 7.4, 0.9, 1H), 7.06 (dd, *J* = 9.5, 8.8, 1H).

2,5-Difluorofluorenone (Compound **24**, Scheme VII): To a flame-dried 100 mL flask containing 3,2'-difluoro-2-biphenic acid (Compound **23**, **Scheme VII**) (2.00 g, 8.54 mmol) in 12 mL benzene was added $SOCl_2$ (1.25 mL, 17.1 mmol, 2.00 equiv) and the mixture was heated to reflux for 90 min. The excess $SOCl_2$ and benzene were removed by distillation at ambient pressure. Benzene (6 mL) and CH_2Cl_2 (5 mL) were then sequentially added and removed by distillation. Anhydrous CH_2Cl_2 (30 mL) was added and the mixture was cooled to -78°C. Trifluoroacetic acid (0.76 mL, 8.54 mmol, 1.00 equiv) was then added and the mixture was allowed to warm to rt overnight. The reaction mixture was poured into 100 mL ice-water, rinsing with 50 mL CH_2Cl_2. The layers were separated and the aqueous phase was extracted with an additional 100 mL CH_2Cl_2. The combined organic extracts were washed successively with sat'd aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give 1.85 g (quantitative) of Compound **24** as a pale yellow solid. Recrystallization (ethanol) afforded Compound **24** as feathery pale yellow needles (mp 149-150°C, literature mp 147.5°C [Namkung et al., "Derivatives of Fluorene XX, Fluorofluorenes, V, New Difluoro-2-acetamidofluorenes for the Study of Carcinogenic Mechanisms", *J. Med. Chem.* **1965**, *8*, 551-554.]).

4,7-Difluoro-2-nitrofluorenone (Compound **25**, **Scheme VII**): 2,5-Difluorofluorenone (Compound **24**, **Scheme VII**) (0.200 g, 0.925 mmol) was added portion-wise to 0.40 mL fuming nitric acid at 0°C in a 5 mL round-bottomed flask. The ice bath was removed and the reaction mixture was gently heated to 50°C for 2 min with a water bath. The reaction mixture was then cooled to rt before the addition of 3.5 mL ice-water. The precipitated product was collected by vacuum filtration, yielding 232 mg (96%) of Compound **25** as a bright yellow solid (mp 207°C, literature mp 207-208°C [Id.]), which was carried on to the next step without further purification.

2-Amino-4,7-difluorofluorenone (Compound **132**, **Scheme VII**): 4,7-Difluoro-2-nitrofluorenone (Compound **25**, **Scheme VII**) (1.00 g, 3.83 mmol) was dissolved in 175 mL ethyl acetate and 10% palladium on carbon was added (10 mol%). The mixture was stirred under an atmosphere of hydrogen gas maintained by a balloon for 105 min, and was then filtered to remove the catalyst, rinsing with an additional 150 mL ethyl acetate. Removal of the solvent under diminished pressure yielded 885 mg (quantitative) of Compound **132** as a dark purple-red solid (mp 236°C, literature mp 234-235°C [Id.]). Data for Compound **132**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.46 (dd, *J* = 8.1, 4.5, 1H), 7.29 (d, *J* = 1.5, 1H), 7.11 (dd, *J* = 8.5, 6.0, 1H), 6.79 (d, *J* = 1.9, 1H), 6.42 dd, *J* = 10.9, 1.9, 1H), 3.99 (br s, 2H).

5,8-Difluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline (structure **19** of **Scheme VI**, where R^2, R^5=F, R^{3-4}, R^6=H, X= C=O): This compound was prepared according to General Method 3 (EXAMPLE 16) from Compound **132** (1.0 g, 4.6 mmol) to afford 5,8-difluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline (structure **19** of **Scheme VI**, where R^2, R^5=F, R^{3-4}, R^6=H). Data for 5,8-difluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline: R_f = 0.49 (silca gel, hexane/EtOAc, 3:1), ^{1}**H NMR** (400 MHz, acetone-d_6) 7.50 (dd, *J* = 8.1, 4.6, 1 H), 7.27 (m, 2 H), 6.73 (s, 1 H), 6.03 (br s, 1 H), 5.47 (s, 1 H), 2.16 (dd, *J* = 7.1, 1.5, 3 H), 1.29 (s, 6 H).

General Method 4: Reduction of a fluorenone (structure **19** of **Scheme VI**) to a 10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (structure **20** of **Scheme VI**): To a flame dried 25-mL r.b. flask equipped with a magnetic stir bar was added structure **19** dissolved in anhydrous CH_2Cl_2 (0.05-0.1 M). The resulting purple solution was cooled to -78°C and to it was added DIBAl-H (1.0 M in hexane, 3-4 equiv) under a blanket of N_2. The resulting light yellow solution was stirred at -78°C for 30 min and to it was then added an excess of $NaSO_4 \cdot 10\ H_2O$ (10-20 equiv). The resulting suspension was warmed to rt during which time the solution became a thick white gel. After stirring for 45 min, the gel was partially dissolved with EtOAc, filtered, and washed repeatedly with EtOAc. The ethyl acetate washes and filtrate were combined and concentrated under reduced pressure to afford structure **20**.

5,8-Difluoro-1,2-dihydro-10-hydroxyl-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **132**, Scheme **VII**): Compound **132** was prepared according to General Method 4 from structure **19** (where R^2,R^5=F, R^{3-4}, R^6=H) (46 mg, 0.15 mmol) and DIBAl-H (1.0 M in hexane, 0.5 mL, 3.2 equiv) to afford 29 mg (62%) of Compound **132** as an off-white solid. Data for Compound **132**: R_f = 0.10 (hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, acetone-d_6) 7.54 (dd, J = 8.3, 5.0, 1 H), 7.24 (dd, J = 8.6, 2.3, 1 H), 7.06 (ddd, J = 11.3, 9.3, 2.5, 1 H), 6.68 (s, 1H), 5.63 (br s, 1 H), 5.44 (d, J = 7.9, 1 H), 5.34 (s, 1 H), 4.79 (d, J = 8.0, 1 H), 2.16 (dd, J = 6.7, 1.2, 3 H), 1.27 (s 3H), 1.25 (s, 3H).

EXAMPLE 33

7,9-Difluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-g]quinoline (Compound **135**, structure **19**, Scheme **VI**, where R^{2-3},R^5=H, R^4,R^6=F, X=CO)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-6,8-difluoro-9-fluorenone (750 mg, 3.2 mmol) to afford 29 mg (2.9%) of Compound **135** as a bright purple solid. Data for Compound **135**: R_f = 0.57 (silica gel, hexane/EtOAc, 3:1). **^{1}H NMR** (400 MHz, acetone-d_6) 7.46 (s, 1 H), 7.22 (dd, J = 8.5, 1.9, 1 H), 6.76 (s, 1 H), 6.68 (ddd, J = 9.6, 5.8, 2.3, 1 H), 5.89 (br s, 1 H), 5.52 (s, 1 H), 2.06 (s, 3 H), 1.30 (s, 6 H).

EXAMPLE 34

7,9-Difluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **133**, structure **20**, **Scheme IV**, where R^{2-3},R^5=H, R^4,R^6=F, X=CHOH)

In a 25 mL r.b. flask equipped with a magnetic stirring bar was dissolved Compound **135** (EXAMPLE 33) (10 mg, 32 µmol) in 6 mL anhydrous CH_2Cl_2. The solution was cooled to -78°C and then DIBALH (0.5 mL, 1.0 M in hexanes) was added. The solution was stirred for 30 min, and then $Na_2SO_4 \cdot 10H_2O$ (150 mg) was added. Upon warming to rt, the suspension congealed to a viscous white gel which was washed with ethyl acetate (4 x 30 mL) and concentrated to afford 9.3 mg (92%) of Compound **133** as an off-white solid. Data for Compound **133**: **^{1}H NMR** (400 MHz, C_6D_6) 7.40 (s, 1 H), 7.09 (dd, *J* = 8.7, 2.1, 1 H), 6.84 (s, 1 H), 6.55 (ddd, *J* = 10, 5.7, 2.0, 1 H), 5.65 (s, 1 H), 5.31 (s, 1 H), 4.54 (d, *J* = 8.5, 1 H), 2.00 (d, *J* = 1.0, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H).

EXAMPLE 35

7,10-Difluoro-1,2-dihydro-2,2,4-trimethyl-5-oxoindeno[2,1-*f*]quinoline (Compound **134**, structure **17** of **Scheme IV**, where R^2, R^5=F, R^1, R^{2-4}, R^6=H, X=C=O)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-4,7-difluoro-9-fluorenone (Compound **132**, **Scheme VII**) (1.0 g, 4.6 mmol) to afford 22 mg (1.6%) of Compound **134** as a purple solid. Data for Compound **134**: R_f = 048 (silica gel, hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, acetone-d_6) 7.47 (m, 1 H), 7.24 (m, 2 H), 6.52 (d, *J* = 11, 1H), 6.12 (br s, 1 H), 5.66 (s, 1 H), 2.25 (d, *J* = 1.5, 3 H), 1.27 (s, 6 H).

EXAMPLE 36

8-Fluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-g]quinoline (Compound **137**, structure **16** of **Scheme IV**, where R^{2-4}, R^6=H, R^5=F, X=C=O)

To a dry 250-mL r.b. flask equipped with a magnetic stir bar and a water-cooled condenser was added 2-amino-7-fluorofluorenone (5.00 g, 23.5 mmol), along with iodine (~ 15 mg) and mesityl oxide (20 mL, 0.175 mol). The resulting red solution was heated at reflux with constant stirring for 2 days. The reaction was followed by TLC (20% ethyl acetate/hexane). After cooling to rt, the crude product mixture was concentrated and purified by silica gel chromatography (400 mL silica, hexane) which afforded an impure sample of Compound **137**. Repurification by silica gel chromatography (hexanes) afforded 64 mg (1%) of Compound **137**. Data for Compound **137**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.53 (m, 1H), 7.36 (s, 1H), 7.21 (dd, *J* = 10, 8, 1H), 7.16 (dd, *J* = 10, 8, 1H), 6.78 (s, 1H), 5.66 (br s, 1H), 5.51 (s, 1H), 2.04 (s, 3H), 1.29 (s, 6H).

EXAMPLE 37

8-Fluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-g]quinoline (Compound **136**, structure **16** of **Scheme IV**, where R^{2-4}, R^6=H, R^5=F, X=CHOH)

This compound was prepared according to General Method 4 (EXAMPLE 34) from Compound **137** (18.2 mg, 0.05 mmol) and DIBALH (1.0 M in hexanes, 0.2 mL) to afford, after purification by PTLC (1000 μm silica, 19/1 hexane/EA) 0.9 mg (5%) of Compound **136** as a white solid. Data for Compound **136**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.52 (m, 1H), 7.37 (s, 1H,), 7.21 (dd, *J* = 8, 2.4, 1H), 7.02 (ddd, *J* = 16, 8, 2.4, 1H), 6,77 (s, 1H), 5.38 (d, *J* =12, 1H), 5.37 (s, 1H,), 5.31 (br s, 1H), 4.59 (d, *J* = 8, 1H), 2.03 (d, *J* =1.2, 3H), 1.28 (s, 3H), 1.26 (s, 3H).

EXAMPLE 38

7-Fluoro-1,2-dihydro-2,2,4-trimethyl-8-nitroindeno[1,2-g]quinoline (Compound **138**, structure **16**, **Scheme IV**, where R^{2-3},R^6=H, R^4=F, R^5= NO_2, X=CH_2)

This compound was prepared according to General Method 3 (EXAMPLE 16) from 2-amino-6-fluoro-7-nitrofluorene (1.00 g, 4.00 mmol) to afford 98 mg (8%) of Compound **138** as a bright purple solid. Data for Compound **138**: R_f = 0.23 (silica gel, hexane/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, acetone-d_6) 8.13 (d, *J* = 8.3, 1 H), 7.66 (d, *J* = 12, 1 H), 6.64 (s, 1 H), 5.47 (s, 1 H), 3.85 (s, 2 H), 2.77 (d, *J* = 1.0, 3 H), 1.36 (s, 6 H).

EXAMPLE 39

5-Chloro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **139**, structure **20**, **Scheme VI**, where R^2=Cl, R^{3-6}=H, X=CHOH).

A solution of 2-amino-4-chloro-9-fluorenol (300 mg, 1.30 mmol), I_2 (~1 mg) and acetone (20 mL) was heated in a sealed tube at 100°C for 16 h. To the cooled reaction mixture was added Celite™ (0.5 g), and the slurry was concentrated *in vacuo* to afford a free-flowing powder which was purified by SGC (230-400 mesh, 2.5 x 15 cm) using a 10-100% EtOAc:hexane gradient to afford 2.6 mg (1%) of Compound **139** as a white solid. Data for Compound **139**: R_f = 0.14 (silica gel, 25% EtOAc:hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 8.18 (d, *J* = 7.7, 1 H), 7.78 (t, *J* = 7.9, 1 H), 7.52 (d, *J* = 7.8, 1 H), 7.19 (t, *J* = 7.8, 1 H), 6.90 (s, 1 H), 5.70 (br s, 1 H), 5.50 (s, 1 H), 5.40 (s, 1 H), 4.59 (d, *J* = 8.5, 1 H), 2.35 (s, 3 H), 1.32 (s, 3 H) and 1.21 (s, 3 H).

EXAMPLE 40

6-Fluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline (Compound **140**, structure **19**, **Scheme VI**, where R^2,R^{4-6}=H, R^3=F, X=CO).

This compound was prepared from 5-fluoro-2-nitrofluorenone (1.0 g, 4.1 mmol) in two steps in the manner previously described for Compound **123** (EXAMPLE 24), affording 0.74 g (61%) of Compound **140** as a dark purple solid. Data for Compound **140**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.33 (s, 1H), 7.26 (m, 3H), 6.75 (s, 1H), 5.45 (s, 1H), 3.96 (br s, 1H), 2.05 (d, *J* = 1.5, 3 H), 1.31 (s, 6H).

EXAMPLE 41

6-Fluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **141**, structure **20**, **Scheme VI**, where R^2,R^{4-6}=H, R^3=F, X=CHOH)

This compound was prepared by General Method 4 from Compound **140** (0.30 g, 1.0 mmol) to afford 0.25 g (84%) of Compound **141** as a pale reddish-purple solid. Data for Compound **141**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.49 (s, 1H), 7.32 (d, *J* = 7.3, 1 H), 7.12 (dt, *J* = 7.8, 4.8, 1 H), 7.00 (dd, *J* = 9.8, 8.3, 1 H), 6.71 (s, 1H), 5.47 (s, 1H), 5.37 (d, *J* = 1.2, 1 H), 3.88 (br s, 1H), 2.06 (d, *J* = 1.2, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H).

EXAMPLE 42

5,8-Difluoro-1,2-dihydro-2,2,4-trimethyl-10-(trifluoroacetoxy)indeno[1,2-*g*]quinoline (Compound **142**, structure **16**, **Scheme IV**, where R^2,R^5=F, R^3,R^4,R^6=H, X=$CHOCOCF_3$)

To a flame-dried 25 mL r.b. flask containing 5,8-difluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline, Compound **132**, EXAMPLE 32, (15.0 mg, 0.048 mmol) in 2 mL dichloromethane at 0°C was added trifluoroacetic anhydride (10 mL, 0.071 mmol, 1.5 equiv) and 4-*N,N*-dimethylaminopyridine (18.0 mg, 0.147 mmol, 3.0 equiv), and the mixture was allowed to stir for 10 min. The reaction mixture was then transferred to a separatory funnel with ethyl acetate (20 mL), pH 7 potassium phosphate buffer (10 mL) was added and the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated under diminished pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 14.1 mg (76%) of Compound **142** as a light yellow oily solid. Data for Compound **142**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.59 (dd, *J* = 8.4, 5.0, 1H), 7.15 (dd, *J* = 8.2, 2.4, 1H), 7.09 (dt, *J* = 8.8, 2.5, 1H), 6.64 (s, 1H), 6.47 (s, 1H), 2.19 (dd, *J* = 6.7, 1.2, 3H), 1.29 (s, 3 H), 1.28 (s, 3 H).

EXAMPLE 43

6-(3,5-Difluorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (Compound **143**, structure **5** of **Scheme 1** where R^1=3,5-difluorophenyl):

A dry 10 mL r.b. flask was charged with Compound **147** (EXAMPLE 47) (17.4 mg, 0.06 mmol) and 0.3 mL ethyl acetate. To this solution was added 10% Pd/C (20 mg). The reaction mixture was stirred under an atmosphere of hydrogen for 1 h. The reaction was purged with nitrogen until all of the hydrogen had been removed from the flask. The product mixture was filtered through a plug of cotton and Celite™ to remove the solids, rinsed with ethyl acetate (50 mL) and concentrated. The crude material was purified by HPLC (reverse phase, ODS semi-preparatory column, 85% methanol/water, 3.0 mL/min). The major peak was isolated and identified as Compound **143** (3.5 mg, 20%) by NMR. Data for Compound **143**: **^{1}H NMR** (400 MHz, methanol-d_4) 7.38 (d, *J* = 2.3, 1H); 7.20 (dd, *J* = 8.5, 1.6, 1H); 7.09 (m, 2H); 6.72 (m, 1H); 6.56 (d, *J* = 8.2, 1H); 2.96 (m, 1H); 1.79 (dd, *J* = 12.9, 5.8, 1H); 1.39 (m, 4H); 1.24 (s, 3H); 1.17 (s, 3H).

EXAMPLE 44

1,2-Dihydro-2,2,4-trimethylindolo[3,2-*g*]quinoline (Compound **144**, structure **16** of **Scheme IV**, where R^{1-6}=H, X=NH)

2-Aminocarbazole (structure **15** of **Scheme IV**, where R^{1-6}=H, X=NH): 2-Nitrocarbazole [Mendenhall, G. D.; Smith, P. A. S. *Org. Syn. Coll. Vol. 5* **1973**, 829, the disclosure of which is herein incorporated by reference] (structure **14** of **Scheme IV**, where R^{1-6}=H, X=NH) (1.0 g, 4.7 mmol) in 50 mL of ethyl acetate was hydrogenated over 10% Pd/C (50 mg) under an atmosphere of hydrogen for 1.5 h at rt giving, after filtration through Celite™, 840 mg (100%) of 2-aminocarbazole. Data for 2-aminocarbazole: ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, *J* = 9.0, 1H), 7.83 (d, *J* = 8.0, 1H), 7.80 (br s, 1H), 7.35 (m, 2H), 7.15 (dd, *J* = 8.2, 1H), 6.67 (d, *J* = 1.8, 1H), 6.58 (dd, *J* = 9.0, 1.8, 1H), 3.73 (br s, 2H).

1,2-Dihydro-2,2,4-trimethylindolo[3,2-*g*]quinoline (Compound **144**, structure **16** of **Scheme IV**, where R^{1-6}=H, X=NH): A solution of 2-aminocarbazole (structure **15** of **Scheme IV**, where R^{1-6}=H, X=NH) (840 mg, 4.7 mmol) in 10 mL of acetone and one crystal (10 mg) of iodine was heated at 100°C for 14 h in a sealed tube. The acetone was removed *in vacuo* to afford a dark oil which was purified by silica gel chromatography (silica gel, hexane/ethyl acetate, 8:2) to afford 738 mg of Compound **144** and 121 mg of 1,2-dihydro-2,2,4-trimethylindolo[2,3-*f*]quinoline (structure **17** of **Scheme IV**, where R^{1-6}=H, X=NH) (71% combined yield). Data for Compound **144**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (d, *J* = 8.0, 1H); 7.80 (br s, 1H), 7.66 (br s, 1H), 7.23 (br s, 2H), 7.12 (m, 1H), 6.30 (br s, 1H), 5.32 (br s, 1H), 3.75 (br s, 1H), 2.13 (s, 3H), 1.39 (s, 1H).

EXAMPLE 45

5-Ethyl-1,2-dihydro-2,2,4-trimethylindolo[2,3-*f*]quinoline (Compound **145**, structure **29** of **Scheme VIII**, where R^{1-6}=H, R^7=Et)

To a suspension of sodium hydride (60% in mineral oil, 16 mg, 0.405 mmol) in 1 mL of THF at 0°C was slowly added 1,2-dihydro-2,2,4-trimethylindolo[2,3-*f*] quinoline (structure **28** of **Scheme VIII**, where R^{1-6}=H) (30 mg, 0.116 mmol) in 1 mL of THF and the resulting mixture was stirred at 0°C for 30 minutes. Iodoethane (9.3 mL, 0.116 mmol) was added dropwise *via* a microsyringe and the reaction mixture was brought to rt and stirred for 16 h. The reaction was quenched with 1 mL of water and extracted with 10 mL of ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to a residue that was purified by flash chromatography (silica gel, hexane/ethyl acetate, 9:1) which gave 27 mg (81%) of Compound **145**. Data for Compound **145**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.81 (d, J = 7.1, 1H), 7.63 (d, J = 8.1; 1H); 7.34 (d, J = 8.0, 1H); 7.25 (br s, 1H); 7.12 (apparent t, J = 7.4, 1H); 6.51 (br s, 1H); 5.38 (br s, 1H); 4.25 (q, J = 7.0, 2H); 4.22 (br s, 1H); 2.16 (s, 3H); 1.26 (s, 6H); 0.91 (t, J = 7.0, 3H).

EXAMPLE 46

6-(3-Chlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **146**, structure **4** of **Scheme II**, where R^1=3-chlorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (91 mg, 0.29 mmol) and 3-bromochlorobenzene (33.6 mg, 0.29 mmol). The crude product was isolated and purified by silica gel chromatography (50 mL silica, 5% ethyl acetate/hexane) and PTLC (reverse phase, 1000 µm plate, 95% methanol/water) to yield 54 mg (81%) of Compound **146**. Data for Compound **146**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.56 (d, J = 4.0, 1H); 7.50 (d, J = 8.0, 1H); 7.34 (apparent t, J = 8.0, 1H); 7.31 (d, J = 4.0, 1H); 7.24 (dd, J = 8.0, 4.0, 1H); 7.23 (dd, J = 8.0, 4.0, 1H); 6.57 (d, J = 8.0, 1H); 5.60 (s, 1H); 2.03 (s, 3H); 1.27 (s, 6H).

EXAMPLE 47

6-(3,5-Difluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **147**, structure **4** of **Scheme II**, where R^1=3,5-difluorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9). From Compound **9** (59.7 mg, 0.19 mmol) and 1-bromo-3,5-difluorobenzene (21.6 mL, 0.19 mmol, Lancaster) a crude reaction mixture was isolated and purified by HPLC (reverse phase, semi-preparative column, 85% methanol/water) to yield 5.6 mg of Compound **147** and 0.9 mg of Compound **148** (EXAMPLE 48) (8% combined yield). Data for Compound **147**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.34 (d, J = 2.2, 1H); 7.28 (dd, J = 8.4, 2.3, 1H);

7.19 (m, 2H); 6.80 (m, 1H); 6.57 (d, J = 8.3, 1H); 5.47 (s, 1H); 5.38 (s, 1H); 2.04 (s, 3H); 1.28 (s, 6H).

EXAMPLE 48

6-(3-Fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **148**, structure **4** of **Scheme II**, where R^1=3-fluorophenyl)

This compound was obtained along with Compound **147** as described above (EXAMPLE 47). Data for Compound **148**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.45 (d, J = 8.0, 1H); 7.35 (m, 2H); 7.26 (dd, J = 7.7, 2.2, 1H); 7.10 (d, J = 2.0, 1H); 7.03 (dd, J = 8.1, 2.0, 1H); 6.54 (d, J = 8.2, 1H); 5.35 (s, 1H); 5.29 (s, 1H); 1.97 (s, 3H); 1.28 (s, 6H).

EXAMPLE 49

1,2-Dihydro-2,2,4-trimethyl-6-(4-pyridyl)quinoline (Compound **149**, structure **4** of **Scheme II**, where R^1=4-pyridyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (23.8 mg, 0.07 mmol) and 4-bromopyridine hydrochloride (14.5 mg, 0.07 mmol, Aldrich). The crude product was isolated and purified by silica gel chromatography (75 mL silica, 5% ethyl acetate/hexane) and recrystallized twice (hexane/CH_2Cl_2, then Et_2O) to afford 7.3 mg (40%) of Compound **149**. Data for Compound **149**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.59 (d, J = 6.0, 2H); 7.55 (m, 2H); 7.45 (d, J = 2.2, 1H); 7.40 (dd, J = 8.3, 2.1, 1H); 6.60 (d, J = 8.2, 1H); 5.40 (s, 1H); 2.06 (s, 3H); 1.30 (s, 6H).

EXAMPLE 50

6-(3-Cyanophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **150**, structure **4** of **Scheme II**, where R^1=3-cyanophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (81.4 mg, 0.26 mmol) and 3-bromobenzonitrile (46.6 mg, 0.26 mmol, Lancaster). The crude product was isolated and purified by silica gel chromatography (75 mL silica, 5% ethyl acetate/hexane) to afford 51.6 mg (74%) of Compound **150** as pale yellow crystals. Data for Compound **150**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.94 (d, *J* = 1.1, 1H); 7.88 (m, 1H); 7.56 (m, 2H); 7.38 (d, *J* = 2.2, 1H,); 7.31 (dd, *J* = 8.3, 2.2, 2H); 6.59 (d, *J* = 8.3, 1H); 5.42 (s, 1H); 5.38 (s, 1H); 2.01 (s, 3H); 1.28 (s, 6H).

EXAMPLE 51

6-(3,5-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 151, structure **4** of **Scheme II**, where R^1=3,5-dichlorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (40.4 mg, 0.13 mmol) and 1-bromo-3,5-dichlorobenzene (28.7 mg, 0.13 mmol, Aldrich). The crude product was isolated and purified by silica gel chromatography (75 mL silica, 5% ethyl acetate/hexane) to afford 32 mg (79%) of Compound **151**. Data for Compound **151**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.53 (d, *J* = 1.8, 2H); 7.34 (d, *J* = 1.8, 1H); 7.27 (m, 2H); 6.57 (d, *J* = 8.3, 1H); 5.38 (s, 1H); 2.04 (s, 3H); 1.28 (s, 6H).

EXAMPLE 52

6-(2,3-Difluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 152, structure **4** of **Scheme II**, where R^1=2,3-difluorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (28.7 mg, 0.09 mmol) and 1-bromo-2,3-difluorobenzene (10 μL, 0.09 mmol, Aldrich). The crude product was isolated and purified by silica gel chromatography (75 mL silica, 5% ethyl acetate/hexane) to afford 16 mg (62%) of Compound **152**. Data for Compound **152**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.21 (m, 5H); 6.57 (d, *J* = 8.3, 1 H); 5.37 (s, 1H); 1.99 (s, 3H); 1.28 (s, 6H).

EXAMPLE 53

1,2-Dihydro-2,2,4-trimethyl-6-(pentafluorophenyl)quinoline (Compound **153**, structure **4** of **Scheme II**, where R^1=pentafluorophenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (55.3 mg, 0.17 mmol) and 1-bromopentafluorobenzene (21.7 mL, 0.17 mmol, Lancaster). The crude product was isolated and purified by silica gel chromatography (75 mL silica, 5% ethyl acetate/hexane) to afford 2.5 mg (5%) of Compound **153**. Data for Compound **153**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.11 (d, *J* = 1.2, 1H); 7.03 (dd, *J* = 8.0, 1.6, 1H); 6.60 (d, *J* = 8.3, 1H); 5.57 (s, 1H); 1.95 (s, 3H); 1.29 (s, 6H).

EXAMPLE 54

1,2-Dihydro-2,2,4-trimethyl-6-[4-(trifluoroacetyl)phenyl]quinoline (Compound **154**, structure **4** of **Scheme II**, where R^1=4-(trifluoroacetyl)phenyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (49.1 mg, 0.15 mmol) and 4'-bromo-2,2,2-trifluoroacetophenone (23.5 µL, 0.15 mmol, Aldrich). The crude product was isolated and purified by silica gel chromatography (75 mL silica, hexane) to afford 50 mg (94%) of Compound **154**. Data for Compound **154**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.06 (dd, *J* = 8.5, 0.8, 2H,); 7.80 (dd, *J* = 8.6, 1.7, 2H); 7.41 (m, 2H); 5.41 (s, 1H); 4.97 (s, 1H); 2.04 (s, 3H); 1.27 (s, 6H).

EXAMPLE 55

1,2-Dihydro-2,2,4-trimethyl-6-(1,3-pyrimid-5-yl)quinoline (Compound **155**, structure **4** of **Scheme II**, where R^1=3,5-pyrimidyl)

This compound was prepared according to General Method 2 (EXAMPLE 9) from Compound **9** (74.4 mg, 0.23 mmol) and 5-bromopyrimidine (37.1 mg, 0.23 mmol, Aldrich). The crude product was isolated and purified by recrystallization (Et_2O/hexanes) to afford 2.1 mg (4%) of Compound **155**. Data for Compound **155**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.97 (s, 1H); 8.94 (s, 2H); 7.39 (d, *J* = 1.9, 1H); 7.32 (dd, *J* = 8.4, 2.2, 1H); 6.63 (d, *J* = 8.3, 1H); 5.39 (s, 1H); 2.05 (s, 3H); 1.29 (s, 6H).

EXAMPLE 56

6-(3-Cyanophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (Compound 156, structure 5 of **Scheme I** where R^1=3-cyanophenyl)

A dry 10 mL r.b. flask was charged with Compound **150** (EXAMPLE 50) (16.7 mg, 0.06 mmol) and 0.5 mL ethyl acetate. To this solution 10% Pd/C (20 mg) was added. The flask was stirred under an atmosphere of hydrogen for 1 h. The reaction was then purged with nitrogen until all of he hydrogen had been removed from the flask. The product mixture was filtered through a plug of cotton and Celite™ to remove the solids, rinsing with ethyl acetate (50 mL). The crude material was purified by HPLC (reverse phase, ODS semi-preparatory column, 85% methanol/water, 3.0 mL/min). The major peak was isolated and identified as Compound **156** (1.8 mg, 11%) by NMR. Data for Compound **156**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.93 (d, *J* = 1.3, 1H); 7.88 (m, 1H); 7.55 (m, 2H); 7.51 (d, *J* = 1.4, 1H); 7.28 (dd, *J* = 8.7, 1.4, 1H); 6.59 (d, *J* = 8.4, 1H); 2.95 (m, 1H); 1.80 (dd, *J* = 12.8, 5.4, 1H); 1.39 (m, 4H); 1.25 (s, 3H); 1.19 (s, 3H).

EXAMPLE 57

5,8-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 157, structure **16 of Scheme IV**, where R^2=R^5=F, R^3=R^4=R^6=H, X=CH_2)

4,7-Difluoro-2-fluorenamine (Namkung, M. J.; Fletcher, T. L.; Wetzel, W. H. Derivatives of Fluorene. XX. Fluorofluorenes. V. New Difluoro-2-acetamidofluorenes for the Study of

Carcinogenic Mechanisms. *J. Med. Chem.* **1965**, *8*, 551-554, the disclosure of which is herein incorporated by reference). To a 25 mL round-bottomed flask containing 4,7-difluoro-9-oxo-2-fluorenamine (EXAMPLE 32) (158.5 mg, 0.686 mmol) in 4.25 mL glacial acetic acid was added red phosphorous (425 mg, 13.7 mmol, 20 equiv) and 57% aqueous HI (0.51 mL). The mixture was heated to reflux for 40 h, then evaporated to near-dryness by distillation. Boiling water (5 mL) was added, and the hot mixture was filtered. Upon addition of 10% NH_4OH (20 mL), a white precipitate formed, and was filtered, washed with water, and dried under vacuum to afford 127 mg (85%) of 4,7-difluoro-2-fluorenamine as a white solid, mp 119-120°C (lit. mp 119.5-121°C). Data for 4,7-difluoro-2-fluorenamine: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.70 (dd, *J* = 8.4, 5.2, 1 H), 7.15 (dd, *J* = 9.0, 2.0, 1 H), 7.03 (app dt, *J* = 9.0, 2.0 ,1 H), 6.63 (s, 1 H), 6.39 (dd, *J* = 11.6, 1.7, 1 H), 3.83 (s, 2 H), 3.80 (br s, 2 H).

5,8-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound **157**, structure **16** of **Scheme IV**, where R^2=R^5=F, R^3=R^4=R^6=H, X=CH_2) This compound was prepared by General Method 3 from 4,7-difluoro-2-fluorenamine (127 mg, 0.58 mmol). Purification by flash column chromatography (silica gel, hexanes / ethyl acetate, gradient elution) afforded 42 mg (24%) of the less polar angular Compound **158** (EXAMPLE 58) as a yellow oil, along with 63 mg (36%) of the more polar Compound **157** as a white solid. Data for Compound **157**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.68 (dd,, *J* = 8.4, 5.3 1 H, 9-H), 7.12 (dd, *J* = 8.8, 2.3, 1 H, 6-H), 7.00 (apparent dt, *J* = 9.1, 2.3, 1 H, 7-H), 6.44 (s, 1 H, 11-H), 5.30 (s, 1 H, 3-H), 3.86 (br s, 1 H, N*H*), 3.78 (s, 2 H, 10-H), 2.22 (dd, *J* = 6.7, 1.5, 3 H, 4-C*H*$_3$), 1.28 [s, 6H, 2-(C*H*$_3$)$_2$].

EXAMPLE 58

7,10-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound **158**, structure **17** of **Scheme IV**, where R^2=R^5=F, R^3=R^4=R^6=H, X=CH_2)

Compound **158** was obtained along with Compound **157** as described above (EXAMPLE 57). Data for Compound **158**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.69 (dd, *J* = 8.3, 5.3, 1 H, 6-

H), 7.11 (dd, J = 8.7, 2.4, 1 H, 9-H), 7.09 (apparent dt, J = 9.1, 2.4, 1 H, 7-H), 6.23 (d, J = 11.0, 1 H, 11-H), 5.34 (s, 1 H, 3-H), 4.08 (s, 2 H, 5-H), 3.84 (br s, 1 H, NH), 2.23 (s, 3 H, 4-CH_3), 1.26 [s, 6 H, 2-(CH_3)$_2$].

EXAMPLE 59

1,2-Dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 159; **Scheme IX**)

The intermediate 2-nitro-3,4-benzocoumarin was prepared by a modified literature procedure. See *J. Org. Chem.*, U.S.S.R., 15 (3), 503 (**1979**), the disclosure of which is herein incorporated by reference. To a flask charged with 2-biphenylcarboxylic acid (5 g, 25 mmol) was added 7 mL of 70 % nitric acid and the resulting yellow slurry was stirred at rt for 30 min. To this slurry 20 mL of fuming nitric acid was introduced dropwise, giving rise to a clear yellow solution. The reaction mixture was stirred at rt for 15 h, and was then poured into ice water (100 mL). The crude mixture was extracted with ethyl acetate (3 x 60 mL) and the combined extracts were washed with water (2 x 20 mL) and brine (2 x 20 mL). Removal of solvent under reduced pressure afforded a crude yellow solid, which was a 2:1 mixture of two regioisomers. The mixture of the dinitrobiphenylcarboxylic acids was dissolved in 80 mL of DMA and the solution was heated at reflux for 12 hours. The reaction was cooled to rt and diluted with 20 mL of water. The desired product precipitated from the solution upon standing at rt overnight. Filtration of the mixture afforded 2.9 g (50%) of 2-nitro-3,4-benzocoumarin, which was used directly in next reaction without further purification. 2-Nitro-3,4-benzocoumarin (2.9 g, 12 mmol) was dissolved in 600 mL of ethyl acetate and treated with 10% Pd/C (1.0 g, 0.94 mmol) and stirred under a hydrogen balloon for 24 h. Filtration of the catalyst and removal of solvent afforded 2.2 g (86%) of 2-amino-3,4-benzocoumarin as a yellowish solid. An Ace-Thred pressure tube charged with 2-amino-3,4-benzocoumarin (2.2 g, 10.4 mmol), iodine (0.8 g, 3.1 mmol) and acetone (150 mL) was sealed. The tube was heated in an oil bath at 80-120 °C for 24 h and then cooled to rt. The dark reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (hexane/EtOAc, 4/1) to give 1.5 g (50%) of Compound **159** as a yellow solid. Data for Compound **159**: mp 190-191 °C; **IR** (KBr)

3352, 2966, 2924, 1712, 1626, 1450, 1356, 1251, 1205; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.90 (d, *J* = 7.8, 1 H), 7.78 (d, *J* = 8.4, 1 H), 7.38-7.22 (m, 3 H), 7.01 (d, *J* = 8.4, 1 H), 5.58 (s, 1 H), 4.31 (br s, 1 H), 2.12 (s, 3 H), 1.33 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) 160.3, 150.5, 145.7, 132.4, 131.6, 128.4, 124.2, 122.0, 121.4, 121.2, 119.3, 118.4, 117.2, 50.8, 29.9, 28.6; **Anal.** Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.19; H, 6.12; N, 4.52.

EXAMPLE 60

(*R/S*)-5-Butyl-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **160**, structure **32** of **Scheme IX** where R=*n*-butyl)

GENERAL METHOD 5: Preparation of compounds of structures **32** and **33** from Compound **159**. This transformation involved a two step sequence: addition of a nucleophile (either a commercial reagent or prepared *in situ* from a metal-halogen exchange reaction), followed by reduction of the resulting cyclic hemiacetal. To a solution of an aryl bromide compound in THF (0.1-0.3 M) at - 78 °C was slowly added 1.1 equiv. of *n*-BuLi (as a hexane solution) and the resulting reaction mixture was allowed to stir at -78°C until the anion was formed. A yellow solution (0.2-0.5 M) of Compound **159** in THF was cannulated into the above solution and the resulting dark red mixture was slowly allowed to warm. As soon as the red color faded (around - 30 °C), the reaction was quenched with water to give a light yellow solution. The reaction mixture was extracted with ethyl acetate and the combined extracts were washed with brine. Removal of solvent under reduced pressure and purification of the crude residue on a silica gel column using a 1:3 mixture of ethyl acetate and hexane as eluents afforded the hemiacetal intermediate as a yellow oil. To a solution of the hemiacetal intermediate in dichloromethane (0.1 M) at - 78°C was added 5-10 equiv of trifluoroacetic acid and triethylsilane (or, alternatively, 2-3 equiv of boron trifluoride etherate and 5-6 equiv of triethylsilane) and the resulting slurry was allowed to warm to rt, giving rise to a dark green solution. The mixture was allowed to stir at rt or reflux in some cases, until the reaction went to completion. The reaction was then quenched with 5% NaOH (aq) and was extracted with ethyl acetate. The combined extracts were washed with brine and concentrated. The crude mixture was purified on a silica gel column using a 1: 5 mixture of ethyl acetate and hexane as eluents, affording the desired product in moderate yield. A second silica gel chromatography was needed in several cases to remove the silane oxide and/or separate the isomers of structures **32** and **33** using a 1:2 mixture of dichloromethane and hexane as eluents.

(*R*/*S*)-5-Butyl-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **160**, structure **32** of **Scheme IX** where R=*n*-butyl) This compound was prepared by General Method 5 from *n*-BuLi (1.6 M, 0.2 mL) and Compound **159** (50 mg, 0.17 mmol) to afford 40 mg (71%) of Compound **160** as a colorless oil. Data for Compound **160**: **IR** (neat) 3388, 2980, 1593, 1468 and 1435 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.62 (d, *J* = 7.8, 1 H), 7.44 (d, *J* = 8.3, 1 H), 7.14 (t, *J* = 7.8, 1 H), 6.98 (t, *J* = 7.8, 1 H), 6.92 (d, *J* = 7.8, 1 H), 6.59 (d, *J* = 8.3, 1 H), 5.88 (dd, *J* = 9.8, 3.1, 1 H), 5.49 (s, 1 H), 3.88 (br s, 1 H), 2.25 (s, 3 H), 1.90-1.79 (m, 1 H), 1.55-1.25 (m, 5 H), 1.28 (s, 3 H), 1.20 (s, 3 H), 0.84 (t, *J* = 7.3, 3 H).

EXAMPLE 61

(*R*/*S*)-1,2-Dihydro-2,2,4-trimethyl-5-phenyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **161**, structure **32** of **Scheme IX**, where R=phenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from bromobenzene (0.15 mL, 1.4 mmol) and Compound **159** (50 mg, 0.17 mmol) to afford 15 mg (25%) of Compound **161** as a colorless oil, along with 6 mg (10%) of Compound **162** (EXAMPLE 62). Data for Compound **161**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.53 (d, *J* = 7.8, 1 H), 7.50 (d, *J* = 8.2, 1 H), 7.22-7.12 (m, 5 H), 7.00 (t, *J* = 7.8, 1 H), 6.92 (s, 1 H), 6.88 (t, *J* = 7.8, 1 H), 6.83 (d, *J* = 7.8, 1 H), 6.69 (d, *J* = 8.2, 1 H), 5.46 (s, 1 H), 3.92 (br s, 1 H), 1.99 (s, 3 H), 1.29 (s, 3 H), 1.26 (s, 3 H).

EXAMPLE 62

(*R/S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-4-methylidene-5-phenyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **162**, structure **33** of **Scheme IX**, where R=phenyl)

This compound (6 mg, 10%) was obtained along with Compound **161** as described above (EXAMPLE 61). Data for Compound **162**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.53 (d, J = 7.3, 1 H), 7.51 (d, J = 8.4, 1 H), 7.24-7.12 (m, 5 H), 6.97 (t, J = 7.3, 1 H), 6.87 (t, J = 7.3, 1 H), 6.80 (d, J = 7.3, 1 H), 6.64 (s, 1 H), 6.59 (d, J = 8.4, 1 H), 4.93 (s, 1 H), 4.64 (s, 1 H), 4.09 (br s, 1 H), 2.44 (d, J = 12.1, 1 H), 2.18 (d, J = 12.1, 1 H), 1.34 (s, 3 H) and 1.13 (s, 3 H).

EXAMPLE 63

(*R/S*)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **163**, structure **32** of **Scheme IX**, where R=4-chlorophenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 4-bromochlorobenzene (1.4 g, 7 mmol) and Compound **159** (0.5 g, 1.7 mmol) to afford 0.27 g (40%) of Compound **163** as a white solid, in addition to 60 mg (9%) of Compound **164** (EXAMPLE 64). Data for Compound **163**: mp 139-140 °C; **IR** (KBr) 3371, 2964, 1593, 1469, 1435 cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) 7.59 (d, J = 7.8, 1 H), 7.56 (d, J = 8.4, 1 H), 7.24 (d, J = 9.1, 2 H), 7.21 (d, J = 9.1, 2 H), 6.98 (t, J = 7.8, 1 H), 6.92 (s, 1 H), 6.86 (t, J = 7.8, 1 H), 6.83 (d, J = 8.4, 1 H), 6.77 (d, J = 7.8, 1 H), 5.54 (br s, 1 H), 5.48 (s, 1 H), 1.99 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 64

(*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound **164**, structure **33** of **Scheme IX**, where R=4-chlorophenyl)

This compound (60 mg, 9%) was obtained along with Compound **163** as described above (EXAMPLE 63). Data for Compound **164**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.53 (d, J = 7.7, 1 H), 7.51 (d, J = 8.3, 1 H), 7.18 (d, J = 8.7, 2 H), 7.15 (d, J = 8.7, 2 H), 6.99 (t, J = 7.7, 1 H), 6.90 (t, J = 7.7, 1 H), 6.79 (d, J = 7.7, 1 H), 6.59 (s, 1 H), 6.58 (d, J = 8.3, 1 H), 4.93 (s, 1 H), 4.59 (s, 1 H), 4.09 (br s, 1 H), 2.43 (d, J = 12.3, 1 H), 2.18 (d, J = 12.3, 1 H), 1.34 (s, 3 H) 1.13 (s, 3 H).

EXAMPLE 65

(*R*/*S*)-5-(4-Fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **165**, structure **32** of **Scheme IX**, where R=4-fluorophenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 4-fluorophenylmagnesium bromide (1.0 M in THF, 1 mL) and Compound **159** (30 mg, 0.1 mmol) to afford 15 mg (38%) of Compound **165** as a colorless oil. Data for Compound **165**: **IR** (KBr) 3360, 2962, 1707, 1601, 1506, 1469, 1221, 1157 cm^{-1}; ^{1}**H NMR** (400 MHz, acetone-d_6) 7.60 (d, *J* = 7.8, 1 H), 7.56 (d, *J* = 8.3, 1 H), 7.26 (dd, *J* = 8.7, 5.7, 2 H), 6.98 (t, *J* = 8.7, 2 H), 6.97 (t, *J* = 7.8, 1 H), 6.92 (s, 1 H), 6.87 (t, *J* = 7.8, 1 H), 6.83 (d, *J* = 8.3, 1 H), 6.76 (d, *J* = 7.8, 1 H), 5.54 (br s, 1 H), 5.47 (s, 1 H), 1.99 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 66

(*R*/*S*)-5-(4-Acetylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **166**, structure **32** of **Scheme IX**, where R=4-acetylphenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 2-(4-bromophenyl)-2-methyl-1,3-dioxane (219 mg, 1.0 mmol) and Compound **159** (30 mg, 0.1 mmol) to afford 4.5 mg (10%) of Compound **166** as a colorless oil. Data for Compound **166**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.83 (d, *J* = 8.3, 2 H), 7.60 (d, *J* = 7.6, 1 H), 7.57 (d, *J* = 8.4, 1 H), 7.36 (d, *J* = 8.3, 2 H), 6.99 (s, 1 H), 6.98 (t, *J* = 7.6, 1 H), 6.89-6.79 (m, 3 H), 5.56 (br s, 1 H), 5.50 (s, 1 H), 2.49 (s, 3 H), 2.00 (s, 3 H), 1.28 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 67

(*R*/*S*)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (Compound **167**, structure **32** of **Scheme IX**, where R=4-methylphenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 4-bromotoluene (171 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 15 mg (58%) of Compound **167** as a colorless oil. Data for Compound **167**: **IR** (KBr) 3362, 2964, 1707, 1593, 1469, 1437, 1259, 1169 cm^{-1}; ^{1}**H NMR** (400 MHz, acetone-d_6) 7.58 (d, *J* = 7.9, 1 H), 7.54 (d, *J* = 8.5, 1 H), 7.10 (d, *J* = 8.0, 2 H), 7.00 (d, *J* = 8.0, 2 H), 6.97 (t, *J* = 7.9, 1

H), 6.89 (s, 1 H), 6.84 (d, *J* = 7.9, 1 H), 6.81 (d, *J* = 8.5, 1 H), 6.75 (d, *J* = 7.9, 1 H), 5.47 (bs, 1 H), 5.45 (s, 1 H), 2.19 (s, 3 H), 1.99 (s, 3 H), 1.25 (s, 3 H), 1.23 (s, 3 H).

EXAMPLE 68

(*R/S*)-1,2-Dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **168**, structure **32** of **Scheme IX**, where R=4-methoxyphenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 4-bromoanisole (187 mg, 1.0 mmol) and Compound **159** (10 mg, 0.03 mmol) to afford 2.5 mg (10%) of Compound **168** as a colorless oil. Data for Compound **168**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.59 (d, *J* = 7.7, 1 H), 7.54 (d, *J* = 8.4, 1 H), 7.13 (d, *J* = 8.7, 2 H), 6.95 (t, *J* = 7.7, 1 H), 6.87 (s, 1 H), 6.86 (d, *J* = 7.7, 1 H), 6.81 (d, *J* = 8.4, 1 H), 6.75 (d, *J* = 8.7, 2 H), 6.74 (t, *J* = 7.7, 1 H), 5.47 (br s, 1 H), 5.45 (s, 1 H), 3.69 (s, 3 H), 1.99 (s, 3 H), 1.25 (s, 3 H), 1.23 (s, 3 H).

EXAMPLE 69

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-[4-(trifluoromethyl)phenyl]-*5H*-chromeno[3,4-*f*]quinoline (Compound **169**, structure **32** of **Scheme IX**, where R=4-(trifluoromethyl)phenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 4-bromobenzotrifluoride (130 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 10 mg (35%) of Compound **169** as a colorless oil. Data for Compound **169**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61-7.56 (m, 4 H), 7.45 (d, *J* = 8.3, 2 H), 7.01 (s, 1 H), 6.97 (d, *J* = 7.7, 1 H), 6.86 (t, *J* = 7.7, 1 H), 6.85 (d, *J* = 8.4, 1 H), 6.81 (d, *J* = 7.7, 1 H), 5.57 (br s, 1 H), 5.49 (s, 1 H), 1.99 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 70

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(thiophen-3-yl)-*5H*-chromeno[3,4-*f*]quinoline (Compound **170**, structure **30** of **Scheme IX**, where R=thiophen-3-yl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 3-bromothiophene (163 mg, 1.0 mmol) and Compound **159** (8 mg, 0.03 mmol) to afford 1.1 mg (11%) of Compound **170** as a colorless oil. Data for Compound **170**: ^{1}**H NMR** (400

MHz, acetone-d_6) 7.60 (d, *J* = 7.3, 1 H), 7.54 (d, *J* = 8.4, 1 H), 7.31 (dd, *J* = 5.0, 3.0, 1 H), 7.08 (d, *J* = 5.0, 1 H), 6.98 (t, *J* = 7.3, 1 H), 6.93 (s, 1 H), 6.89 (t, *J* = 7.3, 1 H), 6.88 (d, *J* = 3.0, 1 H), 6.79 (d, *J* = 8.1, 2 H), 5.48 (br s, 1 H), 2.06 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 71

(-)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound **171**, structure **32** of **Scheme IX**, where R=4-methylphenyl)

This compound was prepared by optical resolution of Compound **167** via HPLC using a chiral column, Chiracel OD-R, using a 9:1 mixture of methanol and water as the mobile phase. The optical purity of Compound **171** was determined by HPLC to be > 99% *e.e.*; $[\alpha]^{20}_D$ = - 246 (MeOH).

EXAMPLE 72

(-)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **172**, structure **32** of **Scheme IX**, where R=4-chlorophenyl)

This compound was prepared by optical resolution of Compound **163** via HPLC using a chiral column, Chiracel OD-R, using a 9:1 mixture of methanol and water as mobile phase. The optical purity of Compound **172** was determined by HPLC to be > 99% *e.e.*; $[\alpha]^{20}_D$ = - 254 (MeOH).

EXAMPLE 73

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(3-methylphenyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound **173**, structure **32** of **Scheme IX**, where R=3-methylphenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 3-bromotoluene (171 mg, 1.0 mmol) and Compound **159** (15 mg, 0.05 mmol) to afford 3.6 mg (19%) of Compound **173** as a colorless oil. Data for Compound **173**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.59 (d, *J* = 7.8, 1 H), 7.54 (d, *J* = 8.4, 1 H), 7.10-6.94 (m, 5 H), 6.89 (s, 1 H), 6.85 (d, *J* = 7.8, 1 H), 6.82 (d, *J* = 8.4, 1 H), 6.77 (d, *J* = 8.0, 1 H), 5.49 (br s, 1 H), 5.46 (s, 1 H), 2.19 (s, 3 H), 2.00 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 74

(+)-(4*l*,5*l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **174**, structure **34** of **Scheme X**, where R=4-chlorophenyl)

Hydrogenation of Compound **163** (15 mg, 0.04 mmol) in the presence of 10% Pd/C (10%) afforded 12 mg (80%) of (*R*/*S*-4*l*,5*l*)-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline as a white solid in addition to 1.1 mg (7%) of Compound **176** (EXAMPLE 76) as a white solid. The enantiomers of (*R*/*S*-4*l*,5*l*)-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline were resolved via HPLC using a chiral column, Chiracel OD-R, using a 9:1 mixture of methanol and water as mobile phase (0.55 mL/min). A 10 mg sample of (*R*/*S*-4*l*,5*l*)-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline afforded 3.1 mg of the first eluting, (+) enantiomer (Compound **174**) (24 min), and 3.0 mg of the second eluting, (-) enantiomer (Compound **175**, EXAMPLE 75) (30 min). The optical purity of Compound **174** was determined by HPLC to be >99% *e.e.* Data for Compound **174**: mp 158-159 °C; **^{1}H NMR** (400 MHz, acetone-d_6) 7.63 (d, *J* = 7.8, 1 H), 7.53 (d, *J* = 8.5, 1 H), 7.24 (s, 4 H), 6.94 (t, *J* = 7.8, 1 H), 6.87 (t, *J* = 7.8, 1 H), 6.76 (d, *J* = 8.5, 1 H), 6.68 (d, *J* = 7.8, 1 H), 6.51 (s, 1 H), 5.10 (br s, 1 H), 3.25 (m, 1 H), 1.89 (dd, *J* = 13.5, 6.4, 1 H), 1.76 (dd, *J* = 13.5, 4.4, 1 H), 1.30 (s, 3 H), 1.21 (s, 3 H), 0.83 (d, *J* = 7.3, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) 150.6, 144.5, 138.6, 134.0, 130.9, 130.5, 128.4, 127.6, 124.9, 123.2, 122.2, 121.9, 120.2, 118.0, 115.8, 74.5, 50.0, 44.3, 31.6, 31.3, 27.5, 22.8. $[\alpha]^{20}_D$ = + 287 (MeOH).

EXAMPLE 75

(-)-(4*l*,5*l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **175**, structure **34** of **Scheme X**, where R=4-chlorophenyl)

This compound was prepared by resolution of (*R*/*S*-4*l*,5*l*)-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline as described above (EXAMPLE 74) via HPLC using a chiral column, Chiracel OD-R, using a 9:1 mixture of methanol and water as mobile phase. The optical purity of Compound **175** was determined by HPLC to be > 95% *e.e.*; $[\alpha]^{20}_D$ = - 260 (MeOH).

EXAMPLE 76

(*R/S*-4*l*,5*u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **176**, structure **35** of **Scheme X**, where R=4-chlorophenyl)

This compound (1.1 mg, 7%) was obtained along with (*R/S*-4*l*,5*l*)-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline as described above (EXAMPLE 75). Data for Compound **176**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.54 (d, *J* = 7.6, 1 H), 7.47 (d, *J* = 8.4, 1 H), 7.15 (d, *J* = 6.5, 2 H), 7.10 (d, *J* = 6.5, 2 H), 7.01 (t, *J* = 7.6, 1 H), 6.89 (t, *J* = 7.6, 1 H), 6.83 (d, *J* = 7.6, 1 H), 6.59 (d, *J* = 8.4, 1 H), 6.47 (s, 1 H), 3.73 (br s, 1 H), 2.82 (m, 1 H), 1.76 (dd, *J* = 13.5, 7.0, 1 H), 1.73 (dd, *J* = 13.5, 4.5, 1 H), 1.46 (d, *J* = 7.1, 3 H), 1.36 (s, 3 H), 1.19 (s, 3 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) 150.5, 143.9, 138.4, 134.0, 130.3, 129.4, 128.6, 127.6, 124.2, 122.6, 122.1, 119.6, 118.0, 115.4, 74.4, 50.1, 42.9, 32.2, 31.8, 27.3, 22.3.

EXAMPLE 77

(*R/S*)-5-(3-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **177**, structure **32** of **Scheme IX**, where R=3-chlorophenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 3-bromochlorobenzene (195 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 14 mg (52%) of Compound **177** as a colorless oil, along with 2.3 mg (7%) of Compound **178** (EXAMPLE 78) as a colorless oil. Data for Compound **177**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61 (d, *J* = 7.8, 1 H), 7.57 (d, *J* = 8.4, 1 H), 7.28-7.18 (m, 4 H), 7.00 (t, *J* = 7.8, 1 H), 6.95 (s, 1 H), 6.89 (d, *J* = 7.8, 1 H), 6.84 (d, *J* = 8.4, 1 H), 6.82 (d, *J* = 8.1, 1 H), 5.58 (br s, 1 H), 5.49 (s, 1 H), 2.01 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 78

(*R/S*)-5-(3-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (Compound **178**, structure **33** of **Scheme IX**, where R=3-chlorophenyl)

This compound (2.3 mg, 7%) was obtained along with Compound **177** as described above (EXAMPLE 77). Data for Compound **178**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61 (d, *J* = 6.7, 1 H), 7.59 (d, *J* = 8.6, 1 H), 7.29-7.20 (m, 4 H), 6.98 (t, *J* = 6.7, 1 H), 6.88 (t, *J* = 6.7, 1

H), 6.79 (d, *J* = 6.7, 1 H), 6.77 (d, *J* = 8.6, 1 H), 6.62 (s, 1 H), 4.99 (s, 1 H), 4.59 (s, 1 H), 2.41 (d, *J* = 12.2, 1 H), 2.27 (d, *J* = 12.2, 1 H), 1.35 (s, 3 H), 1.13 (s, 3 H).

EXAMPLE 79

(*R*/*S*)-5-(4-Bromophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **179**, structure 32 of **Scheme IX**, where R=4-bromophenyl) This compound was prepared by General Method 5 (EXAMPLE 60) from 1,4-dibromobenzene (250 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 16 mg (54%) of Compound **179** as a colorless oil, along with 2.5 mg (8%) of Compound **180** (EXAMPLE 80) as a colorless oil. Data for Compound **179**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.58 (d, *J* = 7.8, 1 H), 7.55 (d, *J* = 8.4, 1 H), 7.39 (d, *J* = 8.5, 2 H), 7.16 (d, *J* = 8.5, 2 H), 6.98 (t, *J* = 7.8, 1 H), 6.90 (s, 1 H), 6.86 (t, *J* = 7.8, 1 H), 6.83 (d, *J* = 8.4, 1 H), 6.77 (d, *J* = 7.8, 1 H), 5.54 (br s, 1 H), 5.47 (s, 1 H), 1.99 (s, 3 H), 1.26 (s, 3 H), 1.23 (s, 3 H).

EXAMPLE 80

(*R*/*S*)-5-(4-Bromophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound **180**, structure 33 of **Scheme IX**, where R=4-bromophenyl) This compound (2.5 mg, 8%) was obtained along with Compound **179** as described above (EXAMPLE 79). Data for Compound **180**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61 (d, *J* = 6.3, 1 H), 7.59 (d, *J* = 8.7, 1 H), 7.41 (d, *J* = 8.5, 2 H), 7.19 (d, *J* = 8.5, 2 H), 6.95 (t, *J* = 6.3, 1 H), 6.86 (t, *J* = 6.3, 1 H), 6.75 (d, *J* = 8.7, 1 H), 6.57 (s, 1 H), 4.97 (s, 1 H), 4.80 (s, 1 H), 2.40 (d, *J* = 12.2, 1 H), 2.26 (d, *J* = 12.2, 1 H), 1.34 (s, 3 H), 1.11 (s, 3 H).

EXAMPLE 81

(*R*/*S*)-5-(3-Bromophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **181**, structure 32 of **Scheme IX**, where R=3-bromophenyl) This compound was prepared by General Method 5 (EXAMPLE 60) from 1,3-dibromobenzene (250 mg, 1.0 mmol) and Compound **159** (15 mg, 0.05 mmol) to afford 13 mg (60%) of Compound **181** as a colorless oil, along with 2.0 mg (9%) of Compound **182** (EXAMPLE 82) as a colorless oil. Data for Compound **181**: **IR** (neat) 3364, 2962, 1699, 1591, 1469, 143 cm^{-1}; ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61 (d, *J* = 7.8, 1 H), 7.57 (d, *J* = 8.4, 1 H), 7.38 (s, 1 H), 7.36 (d, *J*

= 8.5, 1 H), 7.26 (d, *J* = 6.6, 1 H), 7.19 (t, *J* = 7.8, 1 H), 7.00 (t, *J* = 8.3, 1 H), 6.98 (s, 1 H), 6.81-6.90 (m, 3 H), 5.60 (br s, 1 H), 5.50 (s, 1 H), 2.01 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 82

(*R/S*)-5-(3-Bromophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound **182**, structure **33** of **Scheme IX**, where R=3-bromophenyl) This compound (2.0 mg, 9%) was obtained along with Compound **181** as described above (EXAMPLE 81). Data for Compound **182**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.55 (d, *J* = 7.9, 1 H), 7.51 (d, *J* = 8.4, 1 H), 7.28 (d, *J* = 8.0,1 H), 7.12 (d, *J* = 7.9, 1 H), 7.05 (d, *J* = 7.8, 1 H), 7.01 (t, *J* = 7.8, 1 H), 6.92 (t, *J* = 7.4, 1 H), 6.82 (d, *J* = 8.0, 1 H), 6.60 (d, *J* = 8.5, 1 H), 6.59 (s, 1 H), 4.95 (s, 1 H), 4.58 (s, 1 H), 2.43 (d, *J* = 12.3, 1 H), 2.19 (d, *J* = 12.3, 1 H), 1.32 (s, 3 H), 1.14 (s, 3 H).

EXAMPLE 83

(*R/S*)-5-(3,4-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **183**, structure **32** of **Scheme IX**, where R=3,4-dichlorophenyl) This compound was prepared by General Method 5 (EXAMPLE 60) from 1-bromo-3,4-dichlorobenzene (226 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 8.7 mg (30%) of Compound **183** as a colorless oil. Data for Compound **183**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.53 (d, *J* = 7.8, 1 H), 7.50 (d, *J* = 8.3, 1 H), 7.28-7.22 (m, 2 H), 7.20-7.12 (m, 2 H), 6.92 (t, *J* = 7.5, 1 H), 6.85 (d, *J* = 8.2, 1 H), 6.83 (s, 1 H), 6.71 (d, *J* = 8.4, 1 H), 5.48 (s, 1 H), 4.0 (br s, 1 H), 1.97 (s, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H).

EXAMPLE 84

(*R/S*)-5-(3-Bromo-2-pyridyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **184**, structure **32** of **Scheme IX**, where R=3-bromo-2-pyridyl) This compound was prepared by General Method 5 (EXAMPLE 60) from 2,6-dibromopyridine (237 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 20 mg (67%) of Compound **184** as a colorless oil. Data for Compound **184**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.63 (dd, *J* = 7.8, 1.5, 1 H), 7.54 (d, *J* = 8.5, 1 H), 7.52 (d, *J* = 7.8, 1 H), 7.39 (d, *J* = 7.9, 1 H), 7.13 (d, *J*

= 7.6, 1 H), 7.03 (t, *J* = 7.6, 1 H), 6.92-6.80 (m, 4 H), 5.52 (s, 1 H), 5.48 (s, 1 H), 2.03 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 85

(*R/S*)-1,2-Dihydro-5-hydroxy-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **185**, structure **46** of Scheme XIV, where R^1=R^2=H)

To a yellow solution of Compound **159** (20 mg, 0.07 mmol) in 1 mL toluene at -78 °C was added 0.10 mL of DIBALH (1.5 M in toluene, 0.075 mmol) and the resulting solution was stirred at -50 ± 10 °C for 20 min. The reaction was quenched with water (1 mL) and was extracted with ethyl acetate (2 x 5 mL). Removal of solvent and chromatography of the crude residue on a silica gel column using 20% ethyl acetate/hexane as eluents provided 6 mg (30%) of Compound **185** as a colorless oil. Data for Compound **185**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.71 (d, *J* = 7.5, 1 H), 7.53 (d, *J* = 8.4, 1 H), 7.19 (t, *J* = 7.5, 1 H), 7.08 (t, *J* = 7.5, 1 H), 7.07 (d, *J* = 8.4, 1 H), 6.85 (d, *J* = 5.8, 1 H), 6.70 (d, *J* = 7.5, 1 H), 5.52 (s, 1 H), 3.92 (br s, 1 H), 2.94 (d, *J* = 5.8, 1 H), 2.37 (s, 3 H), 1.32 (s, 3 H), 1.20 (s, 3 H).

EXAMPLE 86

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-methoxy-*5H*-chromeno[3,4-*f*]quinoline (Compound **186**, structure **47** of Scheme XIV, where R^1=R^2=H, X=O, R^3=methyl)

To a solution of Compound **185** (25 mg, 0.085 mmol) in MeOH (7 mL) was added a catalytic amount of *p*-toluenesulphonic acid (~0.25 mg) and the solution was allowed to stir at rt for 5 min. The reaction mixture was quenched with a 10% NaOH solution (0.1 mL) then partitioned between EtOAc (10 mL) and water (3 mL). The organic layer was separated and washed with water (3 x 1 mL) and brine (3 x 1 mL) then dried (Na_2SO_4) and concentrated *in vacuo* . The crude product was purified on a 20 x 20 cm, 250 µm. TLC plate, eluting with 25% EtOAc: hexane to afford 8.2 mg (32%) of Compound **186** as a colorless oil. Data for Compound **186**: R_f = 0.28 (silica gel, 25% EtOAc: Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.69 (d, *J* = 7.7, 1 H), 7.48 (d, *J* = 8.3, 1 H), 7.15 (t, *J* = 7.7, 1 H), 7.05 (m, 2 H), 6.65 (d, *J* = 8.3, 1 H), 6.35 (s, 1 H), 5.50 (s, 1 H), 3.90 (br s, 1 H), 3.49 (s, 3 H), 2.28 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H).

EXAMPLE 87

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-propoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound **187**, structure **47** of **Scheme XIV**, where $R^1=R^2=H$, X=O, $R^3=n$-propyl)

This compound was prepared in a manner similar to that of Compound **186** (EXAMPLE 86) from Compound **185** (12 mg) and *n*-propanol to afford 7.2 mg (57%) of Compound **187** as a colorless oil. Data for Compound **187**: $R_f = 0.43$ (silica gel, 25% EtOAc: hexane); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.68 (d, *J* = 7.7, 1 H), 7.49 (d, *J* = 8.3, 1 H), 7.17 (t , *J* = 7.6, 1 H), 7.05 (m, 2 H), 6.65 (d, *J* = 8.4, 1 H), 6.42 (s, 1 H), 5.50 (s, 1 H), 3.90 (br s, 1 H), 3.84 (dt, *J* = 9.2, 6.7, 1 H), 3.54 (dt, *J* = 9.3, 6.8, 1 H), 2.28 (s, 3 H), 1.49 (m, 2 H), 1.33 (s, 3 H), 1.18 (s, 3 H), 0.77 (t, *J* = 7.4, 3 H).

EXAMPLE 88

(*R/S*)-5-Allyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **188**, structure **48** of **Scheme XIV**, where $R^1=R^2=R^4=R^5=R^6=H$)

To a solution of Compound **186** (12 mg, 0.04 mmol) in dichloromethane (1.5 mL) at 0° C was added allyltrimethylsilane (0.005 mL, 0.062 mmol) and TMSOTf (0.01 mL, 0.057 mmol) under nitrogen. The reaction was stirred 5 h at rt. The reaction mixture was concentrated *in vacuo* and purified on a 5x20 cm, 250 µM, TLC plate, eluting with 25 % EtOAc in hexane to afford 2.3 mg (18%) of Compound **188** as a colorless oil. Data for Compound **188**: $R_f = 0.50$ (silica gel, 25% EtOAc: Hexane); ^{1}**H NMR** (400 MHz, acetone-d_6) 7.67 (d, *J* = 7.4, 1 H), 7.49 (d, *J* = 8.3, 1 H), 7.12 (t, *J* = 7.4, 1 H), 6.98 (t, *J* = 7.4, 1 H), 6.87 (d, *J* = 7.4, 1 H), 6.70 (d, *J* = 8.3, 1 H), 5.96-5.85 (m, 2 H), 5.52 (s, 1 H), 5.04 (s, 1 H), 5.00 (d, *J* = 8.6, 1 H), 2.54 (m, 1 H), 2.25 (m, 4 H), 1.27 (s, 3 H), 1.18 (s, 3 H).

EXAMPLE 89

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-propyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **189**, structure **32** of **Scheme IX**, where R=*n*-propyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from a 2.0 M solution of allylmagnesium chloride (0.2 mL, 0.4 mmol) in THF and Compound **159** (25 mg, 0.086 mmol) to afford 5.0 mg (18%) of Compound **189** as a yellow oil. Data for Compound **189**: $R_f = 0.27$ (silica gel, 25% EtOAc: Hexane); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.59 (d, *J* = 7.7,

1 H), 7.43 (d, J = 8.4, 1 H), 7.13 (t, J = 7.7, 1 H), 6.98 (t, J = 7.7, 1 H), 6.91 (d, J = 7.7, 1 H), 6.57 (d, J = 8.4, 1 H), 5.89 (d, J = 10.4, 1 H), 5.49 (s, 1 H), 3.90 (br s, 1 H), 2.25 (s, 3 H), 1.84 (m, 2 H), 1.49-1.35 (m, 2 H), 1.29 (s, 3 H), 1.20 (s, 3 H), 0.89 (t, J = 7.4, 3 H).

EXAMPLE 90

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(2-pyridyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound **190**, structure **32** of **Scheme IX**, where R=2-pyridyl)

To a solution of Compound **184** (10 mg, 0.023 mmol) in 1 mL of THF at - 78 °C was added a 1.0 M hexane solution of *n*-BuLi (0.05 mL, 0.07 mmol), giving rise to a yellow then dark red solution. The mixture was allowed to stir for 15 min and was quenched with water (1 mL). The mixture was extracted with ethyl acetate (2 x 10 mL) and the combined extracts were concentrated. Chromatography of the crude mixture on a silica gel column using 10-30% ethyl acetate / hexane as eluents afforded 7 mg (86%) of Compound **190** as a colorless oil. Data for Compound **190**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.48 (dd, J = 5.4, 1.8, 1 H), 7.61 (dd, J = 7.8, 1.6, 1 H), 7.57 (td, J = 7.8, 1.8, 1 H), 7.54 (d, J = 8.3, 1 H), 7.16-7.13 (m, 2 H), 6.99 (td, J = 7.8, 1.6, 1 H), 6.93 (s, 1 H), 6.88 (td, J = 7.9, 1.0, 1 H), 6.80 (d, J = 8.5, 1 H), 6.77 (dd, J = 7.9, 1.1, 1 H), 5.48 (bs, 1 H), 5.44 (s, 1 H), 1.98 (s, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H).

EXAMPLE 91

(*R/S*)-5-(3-Fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **191**, structure **32** of **Scheme IX**, where R=3-fluorophenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 1-bromo-3-fluorobenzene (175 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 12 mg (47%) of Compound **191** as a colorless oil, along with 1.5 mg (6%) of Compound **192** (EXAMPLE 92) as a colorless oil. Data for Compound **191**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.60 (d, J = 7.9, 1 H), 7.57 (d, J = 8.4, 1 H), 7.26 (td, J = 7.9, 5.9, 1 H), 7.06 (d, J = 7.1, 1 H), 7.01-6.81 (m, 8 H), 5.58 (br s, 1 H), 5.49 (s, 1 H), 2.02 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 92

(*R/S*)-5-(3-Fluorophenyl)-1, 2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5H-chromeno[3,4-*f*]quinoline (Compound **192**, structure **33** of **Scheme IX**, where R=3-fluorophenyl)

This compound (1.5 mg, 6%) was obtained along with Compound **191** as described above (EXAMPLE 91). Data for Compound **192**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.54 (d, *J* = 8.0, 1 H), 7.51 (d, *J* = 8.5, 1 H), 7.15 (td, *J* = 7.9, 5.9, 1 H), 7.06-6.81 (m, 6 H), 6.61 (s, 1 H), 6.59 (d, *J* = 8.0, 1 H), 4.94 (s, 1 H), 4.61 (s, 1 H), 2.43 (d, *J* = 12.3, 1 H), 2.19 (d, *J* = 12.3, 1 H), 1.34 (s, 3 H), 1.14 (s, 3 H).

EXAMPLE 93

(*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-propylthio-*5H*-chromeno[3,4-*f*]quinoline (Compound **193**, structure **47** of **Scheme XIV**, where R^1=R^2=H, X=S, R^3=*n*-propyl)

To a solution of Compound **185** (12 mg, 0.04 mmol) in a 1:1 mixture of 1-propanethiol and methylene chloride (2 mL) was added 2 mg of *p*-TsOH at rt. The reaction was complete after 1 hour by TLC and was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with water and brine then dried over Na_2SO_4. Removal of solvent *in vacuo* followed by purification on a 5x20 cm, 250 µm, TLC plate, eluting with 25% EtOAc:hexane, afforded 14 mg (99%) of Compound **193** as a yellow oil. Data for Compound **193**: R_f = 0.43 (silica gel, 25% EtOAc: Hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 7.69 (d, *J* = 7.6, 1 H), 7.49 (d, *J* = 8.4, 1 H), 7.16 (t , *J* = 7.6, 1 H), 7.05 (t, *J* = 7.6, 1 H), 6.93 (d, *J* = 7.6, 1 H), 6.72 (d, *J* = 8.4, 1 H), 5.51 (s, 1 H), 2.79-2.73 (m, 1 H), 2.62-2.57 (m, 1 H), 2.47 (s, 3 H), 1.70 (m, 2 H), 1.25 (s, 3 H), 1.20 (s, 3 H), 0.99 (t, *J* = 7.3, 3 H).

EXAMPLE 94

(*R/S*)-1,2-Dihydro-5-(3-methoxyphenyl)-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **194**, structure **32** of **Scheme IX**, where R=3-methoxyphenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 3-bromoanisole (187 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 2.6 mg (10%) of

Compound **194** as a colorless oil. Data for Compound **194**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.59 (d, J = 7.8, 1 H), 7.55 (d, J = 8.4, 1 H), 7.12 (t, J = 7.9, 1 H), 6.98 (t, J = 7.2, 1 H), 6.91 (s, 1 H), 6.88-6.71 (m, 6 H), 5.52 (br s, 1 H), 5.47 (s, 1 H), 3.67 (s, 3 H), 2.03 (s, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 95

(*R/S*) 1,2-Dihydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-*5H*-chromeno[3,4-*f*]quinoline (Compound **195**, structure **32** of **Scheme IX**, where R=3-(trifluoromethyl)phenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 3-bromobenzotrifluoride (225 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 10 mg (34%) of Compound **195** as a colorless oil. Data for Compound **195**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61 (d, J = 7.6, 1 H), 7.60 (d, J = 9.0, 1 H), 7.56-7.45 (m, 4 H), 7.04 (s, 1 H), 6.98 (t, J = 7.6, 1 H), 6.89-6.83 (m, 3 H), 5.60 (s, 1 H), 5.55 (s, 1 H), 2.02 (s, 3 H), 1.27 (s, 6 H).

EXAMPLE 96

(*R/S*)-5-(3-Fluoro-4-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **196**, structure **32** of **Scheme IX**, where R=3-fluoro-4-methylphenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 4-bromo-2-fluorotoluene (189 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 15 mg (56%) of Compound **196** as a colorless oil. Data for Compound **196**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.60 (d, J = 7.8, 1 H), 7.56 (d, J = 8.4, 1 H), 7.08 (t, J = 7.9, 1 H), 6.98 (t, J = 7.9, 1 H), 6.94 (d, J = 8.0, 1 H), 6.91 (s, 1 H), 6.90-6.80 (m, 4 H), 5.55 (br s, 1 H), 5.48 (s, 1 H), 2.12 (s, 3 H), 2.01 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 97

(*R/S*)-5-(4-Bromo-3-pyridyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **197**, structure **32** of **Scheme IX**, where R=4-bromo-3-pyridyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 2,5-dibromopyridine (237 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 7 mg (23%) of Compound **197** as a colorless oil. Data for Compound **197**: ^{1}**H NMR** (400 MHz, acetone-d_6) 8.24 (d, *J* = 5.2, 1 H), 7.62 (dd, *J* = 8.0, 1.3, 1 H), 7.57 (d, *J* = 8.4, 1 H), 7.34 (s, 1 H), 7.27 (d, *J* = 6.5, 1 H), 7.06 (td, *J* = 7.4, 1.3, 1 H), 6.97 (s, 1 H), 6.94-6.88 (m, 1 H), 6.86 (d, *J* = 8.4, 1 H), 5.68 (br s, 1 H), 5.55 (s, 1 H), 2.06 (s, 3 H), 1.29 (s, 3 H), 1.28 (s, 3 H).

EXAMPLE 98

(*R/S*)-1, 2-Dihydro-2,2,4-trimethyl-5-(3-pyridyl)-5*H*-chromeno[3,4-*f*]quinoline (Compound **198**, structure **32** of **Scheme IX**, where R=3-pyridyl)

This compound was prepared in a manner similar to that of Compound **190** (EXAMPLE 90), from Compound **197** (5 mg, 0.06 mmol) to afford 4 mg (quant) of Compound **198** as a colorless oil. Data for Compound **198**: ^{1}**H NMR** (400 MHz, acetone-d_6) 8.42 (m, 2 H), 7.58 (dd, *J* = 7.7, 1.3, 1 H), 7.56 (d, *J* = 8.4, 1 H), 7.18 (d, *J* = 5.9, 2 H), 7.01 (t, *J* = 7.8, 1 H), 6.95 (s, 1 H), 6.89-6.83 (m, 3 H), 5.61 (br s, 1 H), 5.52 (s, 1 H), 2.03 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H).

EXAMPLE 99

(*R/S*)-5-(4-Chloro-3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **199**, structure **32** of **Scheme IX**, where R=4-chloro-3-fluorophenyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from 2-chloro-5-bromofluorobenzene (209 mg, 1.0 mmol) and Compound **159** (15 mg, 0.05 mmol) to afford 13 mg (64%) of Compound **199** as a colorless oil. Data for Compound **199**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.61 (dd, *J* = 7.7, 1.4, 1 H), 7.57 (d, *J* = 8.3, 1 H), 7.38 (t, *J* = 7.9, 1 H), 7.13 (dd, *J* = 10.3, 1.8, 1 H), 7.05 (t, *J* = 7.8, 1 H), 7.00 (dd, *J* = 7.7, 1.3, 1 H), 6.93 (s, 1 H), 6.91-6.81 (m, 3 H), 5.62 (br s, 1 H), 5.50 (s, 1 H), 2.02 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H).

EXAMPLE 100

(*R/S*)-1,2-Dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **200**, structure **32** of **Scheme IX**, where R=methyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **159** (8 mg) to afford 4.8 mg (63%) of Compound **200** as a yellow oil. Data for Compound **200**: Rf = 0.44 (silica gel, 25% EtOAc: hexane); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.60 (d, *J* = 7.8, 1 H), 7.43 (d, *J* = 8.4, 1 H), 7.15 (t, *J* = 8.0, 1 H), 7.00 (t, *J* = 8.0, 1 H), 6.91 (d, *J* = 8.1, 1 H), 6.57 (d, *J* = 8.1, 1 H), 6.60 (d, *J* = 6.1, 1 H), 5.49 (s, 1 H), 3.85 (br s, 1 H), 2.26 (s, 3 H), 1.38 (d, *J* = 6.6, 3 H), 1.27 (s, 3 H), 1.22 (s, 3 H).

EXAMPLE 101

(*R/S*)-1,2-Dihydro-5-hexyl-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **201**, structure **32** of **Scheme IX**, where R=*n*-hexyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **159** (8 mg) and 1-iodohexane to afford 4.8 mg (63%) of Compound **201** as a yellow oil. Data for Compound **201**: Rf = 0.33 (silica gel, 25% EtOAc: Hexane); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.59 (d, *J* = 7.8, 1 H), 7.43 (d, *J* = 8.3, 1 H), 7.12 (t, *J* = 7.6, 1 H), 6.98 (t, *J* = 7.4, 1 H), 6.91 (d, *J* = 7.7, 1 H), 6.56 (d, *J* = 8.1, 1 H), 5.86 (d, *J* = 7.4, 1 H), 5.49 (s, 1 H), 2.25 (s, 3 H), 1.83 (m, 2 H), 1.41 (m, 3 H), 1.28 (s, 3 H), 1.20 (s, 3 H), 0.84 (t, *J* = 6.7, 3 H).

EXAMPLE 102

1,2-Dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **202**, structure **32** of **Scheme IX**, where R=H)

To a solution of Compound **185** (EXAMPLE 85) (9.5 mg, 0.03 mmol) in methylene chloride (5 mL) maintained at -78 °C was added trifluoroacetic acid (10 mL) and triethylsilane (25 mL). The reaction mixture was allowed to warm to rt, quenched with 1 N NaOH (3 mL), and partitioned between EtOAc (10 mL) and water (5 mL). The organic layer was washed with brine (3 x 3 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by PTLC (250 µm, 10/1 hexane/EtOAc) afforded 4.6 mg (52%) of Compound **202**. Data for Compound **202**: Rf = 0.36 (silica gel, 25% EtOAc: Hexane); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.58 (d, *J* = 8.0, 1 H), 7.38 (d, *J* = 8.3, 1 H), 7.15 (t, *J* = 8.0, 1 H), 7.02 (t, *J* = 8.0, 1 H), 6.94 (d, *J* = 8.0, 1 H), 6.58 (d, *J* = 8.3, 1 H), 5.47 (s, 1 H), 5.32 (s, 2 H), 3.90 (br s, 1 H), 2.10 (s, 3 H), 1.27 (s, 6 H).

EXAMPLE 103

(*R/S*)-1,2-Dihydro-5-(3-methylbutyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **203**, structure **32** of **Scheme IX**, where R=3-methylbutyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **159** (13 mg) and 1-bromo-3-methylbutane to afford 1 mg (16%) of Compound **203** as a yellow oil. Data for Compound **203**: **TLC:** $R_f = 0.29$ (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.58 (d, $J =$ 8.0, 1 H), 7.43 (d, $J =$ 8.3, 1 H), 7.17 (t, $J =$ 8.1, 1 H), 6.98 (t, $J =$ 8.1, 1 H), 6.91 (d, $J =$ 7.9, 1 H), 6.58 (d, $J =$ 8.0, 1 H), 5.81 (d, $J =$ 8.9, 1 H), 5.49 (s, 1 H), 3.90 (br s, 1 H), 2.24 (s, 3 H), 1.80 (m, 1 H), 1.44 (m, 2 H), 1.28 (m, 5 H), 1.21 (s, 3 H), 0.79 (d, $J =$ 6.2, 3 H), 0.70 (d, $J =$ 6.2, 3 H).

EXAMPLE 104

(*R/S*)-5-(4-Chlorobutyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **204**, structure **32** of **Scheme IX**, where R=4-chlorobutyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **159** (8.3 mg) and 1-bromo-4-chlorobutane to afford 2.2 mg (27%) of Compound **204** as a yellow oil. Data for Compound **204**: $R_f = 0.38$ (silica gel, 25% EtOAc: Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.59 (d, $J =$ 8.0, 1 H), 7.43 (d, $J =$ 8.3, 1 H), 7.13 (t, $J =$ 7.7, 1 H), 7.00 (t, $J =$ 8.4, 1 H), 6.91 (d, $J =$ 7.8, 1 H), 6.57 (d, $J =$ 8.3, 1 H), 5.86 (d, $J =$ 10.4, 1 H), 5.49 (s, 1 H), 3.90 (br s, 1 H), 2.25 (s, 3 H), 1.83 (m, 2 H), 1.41 (m, 4 H), 1.29 (s, 3 H), 1.20 (s, 3 H), 0.84 (t, $J =$ 7.3, 2 H).

EXAMPLE 105

(*R/S*)-5-Benzyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **205**, structure **32** of **Scheme IX**, where R=benzyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **159** (16.8 mg) and benzylmagnesium chloride to afford 2.6 mg (16%) of Compound **205** as a yellow oil. Data for Compound **205**: **TLC:** $R_f = 0.20$ (silica gel, 25% EtOAc: Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.66 (d, $J =$ 7.8, 1 H), 7.48 (d, $J =$ 8.4, 1 H), 7.30-7.15 (m, 6 H), 7.10 (t, $J =$ 7.8, 1 H), 6.89 (d, $J =$ 8.4, 1 H), 6.61 (d, $J =$ 8.4, 1 H), 6.13 (dd, $J =$ 10.2, 3.4, 1 H), 5.49 (s, 1 H), 3.92 (br s, 1 H), 3.11 (dd, *J* = 14.6, 10.2, 1 H), 2.73 (dd, *J* = 14.6, 3.4, 1 H), 2.31 (s, 3 H), 1.54 (s, 3 H), 1.29 (s, 3 H).

EXAMPLE 106

(*R/S*)-5-(4-Bromobutyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **206**, structure **32** of Scheme **IX**, where R=4-bromobutyl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **159** (13.7 mg) and 1,4-dibromobutane to afford 6.0 mg (45%) of Compound **206** as a yellow oil. Data for Compound **206**: R_f = 0.22 (silica gel, 1:1 CH_2Cl_2/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.59 (d, *J* = 8.0, 1 H), 7.44 (d, *J* = 8.3, 1 H), 7.12 (t, *J* = 7.7, 1 H), 6.98 (t, *J* = 8.0, 1 H), 6.93 (d, *J* = 8.0, 1 H), 6.57 (d, *J* = 8.3, 1 H), 5.85 (d, *J* = 10.4, 1 H), 5.49 (s, 1 H), 3.90 (s, 1 H), 2.25 (s, 3 H), 1.83 (m, 2 H), 1.41 (m, 4 H), 1.29 (s, 3 H), 1.20 (s, 3 H), 0.84 (t, *J* = 7.3, 2 H).

EXAMPLE 107

9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **207**, structure **41** of Scheme **XI**, where R^1=H, R^2=F)

5-Fluoro-2-methoxyphenylboronic acid (structure **37** of Scheme **XI**, where R^1=H, R^2=F)

In a 200-mL flask, a solution of 2-bromo-4-fluoroanisole (Aldrich: 4.00 mL, 30.8 mmol) in THF (50 mL) was cooled to -78°C (CO_2/IPA). To this solution *n*-BuLi (Aldrich: 2.5 M in hexanes; 12.4 mL, 31 mmol, 1.0 equivuiv) was added dropwise over a 30 min period. The reaction mixture was stirred at -78°C for 60 min and treated with trimethylborate (Aldrich: 10.5 mL, 92.4 mmol, 3.0 equivuiv). The reaction mixture was allowed to slowly warm to rt, stirred overnight (12 h), and cooled to 0 °C (ice/H_2O). The solution was treated with 5% HCl until the pH reached 6. The reaction mixture was poured into sat'd NH_4Cl (80 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The extracts were washed with sat'd NH_4Cl (1 x 80 mL), combined, dried ($MgSO_4$), filtered through a pad of Celite™, and concentrated to afford 4.90 g (94%) of a white semi-solid. Data for 5-fluoro-2-methoxyphenylboronic acid: **^{1}H NMR** (400 MHz, acetone-d_6): 7.47 (dd, *J* = 8.8, 3.3, 1 H); 7.17 (m, 1 H); 7.05 (dd, *J* = 9.0, 3.9, 1 H); 3.93 (s, 3 H).

Methyl (5'-fluoro-2'-methoxy-4-nitro-2-biphenyl)carboxylate (structure **39** of **Scheme XI**, where R^1=H, R^2=F) In a 250-mL flask, a solution of methyl (2-bromo-5-nitro)benzoate (Compound **38**, **Scheme XI**) (Aldrich: 5.00 g, 19.2 mmol) in DME (60 mL) was treated with tetrakis(triphenylphosphine)palladium (Aldrich: 0.67 g, 0.58 mmol, 3.0 mol%). The reaction mixture was stirred at rt for 10 min. A solution of 5-fluoro-2-methoxyphenylboronic acid (4.90 g, 29 mmol, 1.5 equivuiv) in EtOH (8 mL) was added, followed by 2.0 M Na_2CO_3 (29 mL, 58 mmol, 3 equivuiv). The reaction mixture was heated to 80 °C for 6 h, cooled to rt, poured into 2.0 M Na_2CO_3 (100 mL), and extracted with EtOAc (3 x 100 mL). The extracts were washed with brine (1 x 100 mL), combined, dried ($MgSO_4$), filtered, and concentrated to an orange oil. Purification by SGC (hexane/EtOAc, 10/1) afforded 4.25 g (72%) of methyl (5'-fluoro-2'-methoxy-4-nitro-2-biphenyl)carboxylate as a yellow-orange solid. Data for methyl-(5'-fluoro-2'-methoxy-4-nitro-2-biphenyl)carboxylate: **^{1}H NMR** (400 MHz, $CDCl_3$) 8.73 (d, J = 2.4, 1 H); 8.39 (dd, J = 8.3, 2.4, 1 H); 7.49 (d, J = 8.3, 1 H); 7.09 (td, J = 8.5, 3.1, 1 H); 7.00 (dd, J = 8.5, 3.1, 1 H); 6.85 (dd, J = 8.9, 3.2, 1 H); 3.76 (s, 3 H); 3.70 (s, 3 H).

5'-Fluoro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid In a 200-mL flask, a solution of methyl (5'-fluoro-2'-methoxy-4-nitro-2-biphenyl)carboxylate (4.24 g, 13.9 mmol) in THF (50 mL) was cooled to 0 °C (ice/H_2O) and treated with EtOH (10 mL) and 20% KOH (10 mL). The reaction mixture was allowed to warm to rt and stirred overnight, acidified to pH10 (pH paper) with 10% HCl, and extracted with EtOAc (3 x 75 mL). The extracts were washed with brine (1 x 80 mL), combined, dried ($MgSO_4$), filtered, and concentrated to afford 3.68 g (91%) of 5'-fluoro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid as a yellow solid. Data for 5'-fluoro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid: **^{1}H NMR** (400 MHz, acetone-d_6): 8.68 (d, J = 2.6, 1 H); 8.46 (dd, J = 8.5, 2.6, 1 H); 7.68 (d, J = 8.5, 1 H); 7.16 (m, 2 H); 7.05 (dd, J = 8.8, 4.4, 1 H); 3.73 (s, 3 H).

6-Fluoro-2-nitro-3,4-benzocoumarin In a 250-mL flask, a suspension of 5'-fluoro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid (3.60 g, 12.3 mmol) in dichloroethane (30 mL) was treated with $SOCl_2$ (0.92 mL, 12.6 mmol, 1.0 equivuiv) and heated to a gentle reflux for 90 min. The reaction vessel was cooled to 0 °C (ice/H_2O) and $AlCl_3$ (0.91 g, 6.8 mmol, 0.55 equivuiv) was added portion-wise. The reaction mixture was allowed to slowly warm to rt, stirred 5 h, and quenched with 5% HCl (100 mL). The crude product was extracted with EtOAc (4 x 150 mL). The extracts were washed with sat'd NH_4Cl (1 x 100 mL), combined, dried ($MgSO_4$), filtered, and concentrated to afford 3.19 g (quant) of 6-fluoro-2-nitro-3,4-benzocoumarin as a yellow solid. Data for 6-fluoro-2-nitro-3,4-benzocoumarin: **^{1}H NMR** (400 MHz, DMSO-d_6): 8.84 (d, J = 2.3, 1 H); 8.67 (m, 2 H); 8.40 (d, J = 9.2, 1 H); 7.55 (m, 2 H).

2-Amino-6-fluoro-3,4-benzocoumarin (structure **40** of **Scheme XI**, where R^1=H, R^2=F) In a 500-mL flask, a suspension of 6-fluoro-2-nitro-3,4-benzocoumarin (3.18 g, 12.2 mmol) in EtOAc (300 mL) was treated with 10% Pd/C (2.0 g) and AcOH (0.2 mL), and stirred under an atmosphere of H_2 for 1 h. The reaction mixture was filtered and the solids rinsed with acetone (200 mL). Concentration of the filtrate afforded 2.19 g (78%) of 2-amino-6-fluoro-3,4-benzocoumarin as a yellow solid. Data for 2-amino-6-fluoro-3,4-benzocoumarin: **^{1}H NMR** (400 MHz, acetone-d_6): 8.09 (d, J = 8.6, 1 H); 7.86 (dd, J = 9.8, 3.0, 1 H); 7.55 (d, J = 2.6, 1 H); 7.33 (dd, J = 9.2, 4.9, 1 H); 7.28 (dd, J = 9.2, 2.6, 1 H); 7.17 (dt, J = 3.0, 9.0).

9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-isocoumarino[3,4-*f*]quinoline (Compound **207**, structure **41** of **Scheme XI**, where R^1=H, R^2=F) In a 200-mL resealable pressure tube, a suspension of 2-amino-6-fluoro-3,4-benzocoumarin (1.10 g) in acetone (100 mL) was treated with iodine (Aldrich: 0.50 g) and heated to 110 °C for 32 h. The reaction mixture was cooled to rt, concentrated to remove the bulk of the acetone, and dissolved in CH_2Cl_2 (200 mL). The organic layer was washed with 0.5 N $Na_2S_2O_3$ (2 x 200 mL) and sat'd $NaHCO_3$ (1 x 100 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afforded an orange solid. Purification by SGC (hexane/EtOAc, 5/1) afforded 0.51 g (34%) of Compound **207** as a bright yellow solid. Data for Compound **207**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.96 (d, J = 8.6, 1 H); 7.83 (dd, J = 10.0, 2.9, 1 H); 7.30 (dd, J = 9.0, 4.9, 1 H); 7.22 (d, J = 8.6, 1 H); 7.17 (m, 1 H); 6.25 (br s, 1 H); 5.54 (s, 1 H); 1.30 (s, 6 H). The acetone multiplet obscures the C(4) methyl group.

EXAMPLE 108

8-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **208**, structure **41** of **Scheme XI**, where R^1=F, R^2=H)

2-Bromo-5-fluoroanisole (structure **36** of **Scheme XI**, where R^1=F, R^2=H) In a 250 mL r.b. flask, a solution of 2-bromo-5-fluorophenol (Lancaster: 7.0 mL, 64 mmol, 1.0 equivuiv) in acetone (140 mL) was treated with iodomethane (Aldrich: 4.8 mL, 77 mmol, 1.2 equivuiv), potassium carbonate (8 g), and water (1 mL). The reaction mixture was heated at reflux for 6 h, cooled to rt, clarified with H_2O (40 mL), and the bulk of the volatiles was removed under reduced pressure. The reaction mixture was extracted with EtOAc (3 x 120 mL); the extracts were washed with brine (1 x 80 mL), combined, dried (K_2CO_3), filtered, and concentrated to a clear oil. Bulb-to-bulb distillation (60-65 °C, 0.7 Torr) afforded 13.22 g (quant) of 2-bromo-5-fluoroanisole as a colorless liquid. Data for 2-bromo-5-fluoroanisole: **^{1}H NMR** (400 MHz, $CDCl_3$): 7.46 (dd, *J* = 10.6, 8.7, 1 H); 6.64 (dd, *J* = 10.4, 2.8, 1 H); 5.58 (dt, *J* = 10.4, 2.4, 1 H); 3.88 (s, 3 H).

4-Fluoro-2-methoxyphenylboronic acid (structure **37** of **Scheme XI**, where R^1=F, R^2=H) In a 100 mL r.b. flask, a solution of 2-bromo-5-fluoroanisole (5.50 g, 26.8 mmol, 1.0 equivuiv) in THF (30 mL) was cooled to -78°C (CO_2/IPA) and *n*-BuLi (2.5 M in hexanes; 10.7 mL, 27 mmol, 1.0 equivuiv) was added via syringe over a 15 min period. The reaction mixture was stirred at -78°C for 45 min. Trimethylborate (Aldrich: 9.1 mL, 80 mmol, 3.0 equivuiv) was added slowly via syringe. The reaction mixture was allowed to warm to rt, stirred an additional 10 h, and cooled to 0 °C. The reaction mixture was brought to pH6 with 5% HCl, poured into sat'd NH_4Cl (60 mL), and extracted with methylene chloride (3 x 80 mL). The extracts were washed with sat'd NH_4Cl (1 x 50 mL), combined, dried ($MgSO_4$), filtered, and concentrated to afford 4.22 g (93%) of crude 4-fluoro-2-methoxyboronic acid as a white solid, which was used without further purification.

7-Fluoro-2-nitro-3,4-benzocoumarin In a 200 mL r.b. flask, a solution of 2-bromo-5-nitrobenzoic acid (Compound **43**, **Scheme XII**) (Aldrich: 4.10 g, 16.7 mmol, 1.0 equivuiv) in DME (65 mL) was treated with tetrakis(triphenylphosphine) palladium (Aldrich: 0.58 g, 0.50 mmol, 3.0 mol%). The reaction mixture was stirred at rt for 10 min. A solution of 4-

fluoro-2-methoxyphenylboronic acid (4.20 g, 25 mmol, 1.5 equivuiv) in EtOH (10 mL) was added, followed by 2.0 M Na_2CO_3 (30 mL). The reaction mixture was heated to 80°C for 6 h, cooled to rt, poured into 5% HCl (100 mL), and extracted with EtoAc (3 x 100 mL). The extracts were washed with sat'd NH_4Cl (1 x 100 mL) and brine (1 x 100 mL), combined, dried ($MgSO_4$), filtered, and concentrated to an orange solid. This crude material, consisting of impure 4'-fluoro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid (structure **44** of **Scheme XII**, where R^1=F, R^2=H), was suspended in 1,2-dichloroethane (80 mL), treated with thionyl chloride (1.2 mL), and heated at reflux for 90 min. The reaction mixture was cooled to rt, treated with aluminum trichloride (0.4 g), and allowed to react overnight (11 h). The reaction mixture was poured into 20% KOH (80 mL) and extracted with methylene chloride (3 x 80 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated to an orange oil. The crude material was dissolved in methylene chloride (50 mL), adsorbed onto Celite™ (1 g), and concentrated to a fluffy orange powder. This powder was applied to a pad of silica gel in a 250 mL Buchner funnel (50 x 50 mm). The pad was rinsed with 100 mL of 2:1 hexane:EtOAc, which was discarded, and then 400 mL of 1:1 hexane:EtOAc. The filtrate was concentrated to afford 2.08 g (48%) of 7-fluoro-2-nitro-3,4-benzocoumarin as an orange solid. Data for 7-fluoro-2-nitro-3,4-benzocoumarin: **^{1}H NMR** (400 MHz, acetone-d_6) 9.02 (d, *J* = 2.4, 1 H); 8.71 (dd, *J* = 8.8, 2.4, 1 H); 8.65 (d, *J* = 8.8, 1 H); 8.53 (dd, *J* = 9.6, 6.1, 1 H); 7.34 (m, 2 H).

2-Amino-7-fluoro-3,4-benzocoumarin (structure **40** of **Scheme XII**, where R^1=F, R^2=H) In a 250-mL flask, a suspension of 7-fluoro-2-nitro-3,4-benzocoumarin (2.04 g, 7.9 mmol) in EtOAc (150 mL) was treated with 10% Pd/C (1.2 g) and AcOH (0.2 mL), and stirred under an atmosphere of H_2 for 1 h. The reaction mixture was filtered and the solids rinsed with acetone (200 mL). Concentration of the filtrate afforded 1.61 g (89%) of 2-amino-7-fluoro-3,4-benzocoumarin as a yellow solid. Data for 2-amino-7-fluoro-3,4-benzocoumarin: **^{1}H NMR** (400 MHz, acetone-d_6) 8.15 (dd, *J* = 9.6, 6.1, 1 H); 8.05 (d, *J* = 8.6, 1 H); 7.55 (d, *J* = 2.5, 1 H); 7.28 (dd, *J* = 8.6, 2.5, 1 H); 7.14 (m, 1 H); 7.12 (d, *J* = 9.6, 1 H); 5.4 (br s, 2 H).

8-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **208**, structure **39** of **Scheme XI**, where R^1=F, R^2=H) In a 200-mL resealable pressure tube, a suspension of 2-amino-7-fluoro-3,4-benzocoumarin (1.61 g) in acetone (100 mL) was treated with iodine (Aldrich: 0.50 g) and heated to 110°C for 32 h. The reaction mixture was cooled to rt, concentrated to remove the bulk of the acetone, and dissolved in CH_2Cl_2 (200 mL). The organic layer was washed with 0.5 N $Na_2S_2O_3$ (2 x 200 mL) and sat'd $NaHCO_3$ (1 x 100 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afford an orange solid. Purification by SGC (hexane/EtOAc, 5/1) afforded 0.46 g (21%) of Compound **208** as a bright yellow solid. Data for Compound **208**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.12 (dd, *J* = 9.6, 5.9, 1 H); 7.92 (d, *J* = 9.6, 1 H); 7.22 (d, *J* = 8.6, 1 H); 7.11 (m, 2 H); 6.1 (br s, 1 H); 5.53 (d, *J* = 1.2, 1 H); 1.29 (s, 6 H). The acetone multiplet obscures the C(4) methyl group.

EXAMPLE 109

9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **209**, structure **41** of Scheme **XI**, where R^1=H, R^2=Cl)

2-Bromo-4-chloroanisole (structure **36** of Scheme **XI**, where R^1=H, R^2=Cl) In a 250 mL r.b. flask, a solution of 2-bromo-4-chlorophenol (Lancaster: 16.94 g, 81.6 mmol, 1.0 equivuiv) in acetone (160 mL) was treated sequivuentially with iodomethane (6.10 mL, 98 mmol, 1.2 equivuiv), potassium carbonate (12 g), and water (4 mL). The reaction mixture was heated at reflux for 3 h, cooled to rt, and the bulk of the volatiles was removed under reduced pressure. The residue was poured into water (140 mL) and extracted with EtOAc (3 x 150 mL). The extracts were washed with brine (1 x 100 mL), combined, dried (K_2CO_3), filtered through a pad of Celite™, and concentrated to a clear oil. Short-path distillation (80-85 °C, 1 Torr) afforded 17.74 g (98%) of 2-bromo-4-chloroanisole as a clear liquid. Data for 2-bromo-4-chloroanisole: **^{1}H NMR** (400 MHz, acetone-d_6) 7.53 (d, *J* = 2.5, 1 H); 7.24 (dd, *J* = 9.7, 2.5, 1 H); 6.81 (d, *J* = 9.7, 1 H); 3.88 (s, 3 H).

5-Chloro-2-methoxyphenylboronic acid (structure **37** of Scheme **XI**, where R^1=H, R^2=Cl) This compound was prepared in a manner similar to that of 5-fluoro-2-methoxyphenylboronic acid (EXAMPLE 107) from 2-bromo-4-chloroanisole (2.00 g, 9.0 mmol, 1.0 equivuiv), *n*-BuLi (2.5 M in hexanes; 3.62 mL, 9.0 mmol, 1.0 equivuiv), and trimethylborate (3.0 mL, 26 mmol, 2.9 equivuiv) to afford 1.30 g (77%) of crude 5-chloro-2-methoxyphenylboronic acid as a white semi-solid. This compound was used in the next reaction with no further purification.

Methyl (5'-chloro-2'-methoxy-4-nitro-2-biphenyl)carboxylate (structure 39 of Scheme XI, where R^1=H, R^2=Cl) This compound was prepared in a manner similar to that of methyl-(5'-fluoro-2'-methoxy-4-nitro-2-biphenyl)carboxylate (EXAMPLE 107) from methyl 2-bromo-5-nitrobenzoate (1.25 g, 4.8 mmol, 1.0 equivuiv), tetrakis(triphenylphosphine) palladium (Aldrich: 0.16 g, 0.14 mmol, 2.9 mol%), and 5-chloro-2-methoxyphenylboronic acid (1.30 g, 6.9 mmol, 1.5 equivuiv) to afford 0.85 g (55%) of methyl-5'-chloro-2'-methoxy-4-nitro-2-biphenylcarboxylate as a yellow-orange solid. Data for methyl-5'-chloro-2'-methoxy-4-nitro-2-biphenylcarboxylate: **^{1}H NMR** (400 MHz, $CDCl_3$): 8.73 (d, J = 2.4, 1 H); 8.38 (dd, J = 8.5, 2.5, 1 H); 7.49 (d, J = 8.5, 1 H); 7.36 (dd, J = 8.7, 2.5, 1 H); 7.23 (d, J = 2.5, 1 H); 6.85 (d, J = 8.7, 1 H); 3.76 (s, 3 H); 3.70 (s, 3 H).

5'-Chloro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid This compound was prepared in a manner similar to that of 5'-fluoro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid (EXAMPLE 107) from methyl-5'-chloro-2'-methoxy-4-nitro-2-biphenylcarboxylate (0.83 g, 2.6 mmol) to afford 0.75 g (95%) of 5'-chloro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid as a yellow solid. Data for (5'-chloro-2'-methoxy-4-nitro-2-biphenyl)carboxylic acid: **^{1}H NMR** (400 MHz, acetone-d_6) 8.69 (d, J = 2.5, 1 H); 8.46 (dd, J = 8.3, 2.6, 1 H); 7.68 (d, J = 8.5, 1 H); 7.41 (dd, J = 8.9, 2.7, 1 H); 7.33 (d, J = 2.8, 1 H); 7.08 (d, J = 8.6, 1 H); 3.75 (s, 3 H).

6-Chloro-2-nitro-3,4-benzocoumarin This compound was prepared in a manner similar to that of 6-fluoro-2-nitro-3,4-benzocoumarin (EXAMPLE 107) from 5'-chloro-2'-methoxy-4-nitro-2-biphenylcarboxylic acid (0.74 g, 2.3 mmol), $SOCl_2$ (0.17 mL, 2.3 mmol), and $AlCl_3$ (0.30 g, 2.5 mmol) to afford 0.64 g (quant) of 6-chloro-2-nitro-3,4-benzocoumarin as a yellow solid. Data for 6-chloro-2-nitro-3,4-benzocoumarin: **^{1}H NMR** (400 MHz, acetone-d_6) 9.04 (d, J = 2.3, 1 H); 8.73 (m, 2 H); 8.51 (d, J = 2.4, 1 H); 7.72 (dd, J = 8.6, 2.4, 1 H); 7.50 (d, J = 8.7, 1 H).

2-Amino-6-chloro-3,4-benzocoumarin (structure **40** of **Scheme XI**, where R^1=H, R^2=Cl) This compound was prepared in manner similar to that of 2-amino-6-fluoro-3,4-benzocoumarin from 6-chloro-2-nitro-3,4-benzocoumarin (0.64 g, 2.3 mmol) to afford 0.50 g (88%) of 2-amino-6-chloro-3,4-benzocoumarin as a yellow solid. Data for 2-amino-6-chloro-3,4-benzocoumarin: **^{1}H NMR** (400 MHz, acetone-d_6) 8.11 (m, 2 H); 7.55 (d, *J* = 2.5, 1 H); 7.39 (dd, *J* = 8.6, 2.5, 1 H); 7.28 (m, 2 H).

9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **209**, structure **41** of **Scheme XI**, where R^1=H, R^2=Cl) This compound was prepared in a manner similar to that of Compound **207** from 2-amino-6-chloro-3,4-benzocoumarin (0.50 g) to afford 0.14 g (21%) of Compound **209** as a bright yellow solid. Data for Compound **209**: **^{1}H NMR** (400 MHz, acetone-d_6): 8.10 (d, *J* = 2.4, 1 H); 8.00 (d, *J* = 8.7, 1 H); 7.39 (dd, *J* = 8.7, 2.3, 1 H); 7.26 (d, *J* = 8.8, 1 H); 7.23 (d, *J* = 8.6, 1 H); 5.55 (s, 1 H); 1.30 (s, 6 H). The acetone multiplet obscures the C(4) methyl group.

EXAMPLE 110

(*R/S*)-5-Butyl-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **210**, structure **42** of **Scheme XI**, where R=*n*-butyl, R^1=H, R^2=F)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **207** (0.53 g, 1.7 mmol) and *n*-BuLi (2.5 M in hexanes, 2.7 mL, 6.8 mmol, 4.0 equivuiv) to afford 0.34 g (57%) of Compound **210** as a yellow foam. Data for Compound **210**: **^{1}H NMR** (400 MHz, acetone-d_6): 7.54 (d, *J* = 8.5, 1 H); 7.49 (dd, *J* = 10.2, 2.9, 1 H); 7.03 (dd, *J* = 8.8, 4.9, 1 H); 6.88 (dt, *J* = 2.9, 8.8, 1 H); 6.75 (d, *J* = 8.5, 1 H); 5.80 (br s, 1 H); 5.49 (s, 1 H); 4.83 (t, *J* = 7.6, 1 H); 2.36 (q, *J* = 7.5, 2 H); 2.05 (s, 3 H); 1.46 (sextet, *J* = 7.4, 2 H); 1.10 (br s, 8H); 0.93 (t, *J* = 7.4, 3 H).

EXAMPLE 111

(*R/S*)-5-Butyl-8-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **211**, structure **42** of **Scheme XI**, where R=*n*-butyl, R^1=F, R^2=H)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **208** (29 mg, 0.09 mmol) and *n*-BuLi (2.5 M in hexanes, 0.16 mL, 0.40 mmol) to afford 6.5 mg (20%) of Compound **211** as a yellow foam. Data for Compound **211**: **^{1}H NMR** (400 MHz, acetone-d_6): 7.77 (dd, *J* = 8.7, 6.3, 1 H); 7.51 (d, *J* = 8.5, 1 H); 6.85 (m, 3 H); 5.80 (br s, 1 H); 5.49 (s, 1 H); 4.84 (t, *J* = 7.5, 1 H); 2.37 (q, *J* = 7.5, 2 H); 2.07 (s, 3 H); 1.47 (sextet, *J* = 7.4, 2 H); 1.10 (br s, 8H); 0.93 (t, *J* = 7.4, 3 H).

EXAMPLE 112

(*R/S*)-5-(3-Chlorophenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **212**, structure **42** of **Scheme XI**, where R=3-chlorophenyl, R^1=H, R^2=F)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **207** (50 mg, 0.16 mmol) and 3-bromochlorobenzene (120 mL) to afford 46 mg (70%) of Compound **212** as a colorless solid. Data for Compound **212**: **^{1}H NMR** (400 MHz, acetone-d_6): 7.56 (d, *J* = 8.4, 1 H); 7.36 (dd, *J* = 9.8, 2.9, 1 H); 7.25 (m, 4 H); 6.95 (s, 1 H); 6.85 (d, *J* = 8.5, 1 H); 6.81 (m, 1 H); 6.74 (td, *J* = 8.5, 2.9, 1 H); 5.51 (s, 1 H); 2.00 (d, *J* = 1.0, 3 H); 1.28 (s, 3 H); 1.26 (s, 3 H).

EXAMPLE 113

(*R/S*)-5-(4-Chloro-3-methylphenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **213**, structure **42** of **Scheme XI**, where R=4-chloro-3-methylphenyl, R^1=H, R^2=F)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **207** (50 mg, 0.16 mmol) and 5-bromo-2-chlorotoluene (0.21 g) to afford 42 mg (62%) of Compound **213** as a colorless solid. Data for Compound **213**: **^{1}H NMR** (400 MHz, acetone-d_6): 7.55 (d, *J* = 8.4, 1 H); 7.34 (dd, *J* = 10.0, 2.8, 1 H); 7.22 (m, 2 H); 7.00 (br d, *J* = 10.3, 1 H); 6.89 (s, 1 H); 6.84 (d, *J* = 8.4, 1 H); 6.75 (m, 2 H); 5.49 (s, 1 H); 2.24 (s, 3 H); 1.99 (d, *J* = 1.2, 3 H); 1.27 (s, 3 H); 1.25 (s, 3 H).

EXAMPLE 114

(*R/S*)-5-(4-Chlorophenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **214**, structure **42** of **Scheme XI**, where R=4-chlorophenyl, R^1=H, R^2=F)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **207** (50 mg, 0.16 mmol) and 4-bromochlorobenzene (0.19 g) to afford 33 mg (50%) of Compound **214** as a pale yellow oil. Data for Compound **214**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.55 (d, *J* = 8.4, 1 H); 7.34 (dd, *J* = 10.0, 2.8, 1 H); 7.27 (d, *J* = 8.6, 2 H); 7.22 (d, *J* = 8.6, 2 H); 6.92 (s, 1 H); 6.84 (d, *J* = 8.5, 1 H); 6.75 (m, 2 H); 5.60 (br s, 1 H); 5.48 (d, *J* = 1.3, 1 H); 1.99 (d, *J* = 1.3, 3 H); 1.27 (s, 3 H); 1.24 (s, 3 H).

EXAMPLE 115

(*R/S*)-9-Fluoro-1,2-dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **215**, structure **42** of **Scheme XI**, where R=4-methoxyphenyl, R^1=H, R^2=F)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **207** (50 mg, 0.16 mmol) and 4-bromoanisole (0.13 mL) to afford 8 mg (12%) of Compound **215** as a pale yellow oil. Data for Compound **215**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.53 (d, *J* = 8.4, 1 H); 7.34 (dd, *J* = 10.0, 2.8, 1 H); 7.11 (d, *J* = 8.8, 2 H); 6.86 (s, 1 H); 6.82 (d, *J* = 8.4, 1 H); 6.76 (d, *J* = 8.6, 2 H); 6.70 (m, 2 H); 5.6 (br s, 1 H); 5.46 (s, 1 H); 3.70 (s, 3 H); 1.99 (s, 3 H); 1.26 (s, 3 H); 1.23 (s, 3 H).

EXAMPLE 116

(*R/S*)-8-Fluoro-1,2-dihydro-5-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **216**, structure **47** of **Scheme XIV**, where R^1=F, R^2=H, R^3=methyl, X=0)

(*R/S*)-8-Fluoro-1,2-dihydro-5-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (structure **46** of **Scheme XIV**, where R^1=F, R^2=H) This compound was prepared in a manner similar to that of Compound **185** (EXAMPLE 85) from Compound **208** (170 mg) and DIBALH (1.0 M in hexane; 1.25 mL) to afford 27 mg (16%) of (*R/S*)-8-fluoro-1,2-dihydro-5-hydroxyl-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline as a white solid. Data for

(*R/S*)-8-fluoro-1,2-dihydro-5-hydroxy-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline: ^{1}H NMR (400 MHz, acetone-d_6): 7.74 (dd, *J* = 8.6, 6.3, 1 H); 7.50 (d, *J* = 8.4, 1 H); 6.85 (s, 1 H); 6.79 (m, 2 H); 6.72 (dd, *J* = 9.9, 2.7, 1 H); 5.51 (d, *J* = 1.2, 1 H); 2.82 (s, 3 H); 1.30 (s, 3 H); 1.17 (s, 3 H).

(*R/S*)-8-Fluoro-1,2-dihydro-5-methoxy-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **216**, structure **47** of **Scheme XIV**, where R^1=F, R^2=H, R^3=methyl, X=0) This compound was prepared in a manner similar to that of Compound **186** (EXAMPLE 86) from (*R/S*)-8-fluoro-1,2-dihydro-5-hydroxy-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (24 mg) to afford 25 mg (quant) of Compound **216** as a white solid. Data for Compound **216**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.74 (dd, *J* = 8.5, 6.2, 1 H); 7.50 (d, *J* = 8.4, 1 H); 6.85 (m, 2 H); 6.79 (d, *J* = 8.4, 1 H); 6.38 (s, 1 H); 5.52 (t, *J* = 1.0, 1 H); 3.46 (s, 3 H); 2.26 (d, *J* = 1.2, 3 H); 1.31 (s, 3 H); 1.15 (s, 3 H).

EXAMPLE 117

(*R/S*)-5-(4-Chlorophenyl)-8-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **217**, structure **42** of **Scheme XI**, where R=4-chlorophenyl, R^1=F, R^2=H)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **208** (42 mg, 0.13 mmol) and 4-bromochlorobenzene (0.19 g) to afford 10 mg (18%) of Compound **217** as a pale yellow oil. Data for Compound **217**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.62 (dd, *J* = 8.6, 6.3, 1 H); 7.53 (d, *J* = 8.4, 1 H); 7.27 (d, *J* = 8.7, 2 H); 7.23 (d, *J* = 8.7, 2 H); 6.96 (s, 1 H); 6.83 (d, *J* = 8.2, 1 H); 6.67 (m, 1 H); 6.58 (dd, *J*= 8.7, 2.5, 1 H); 5.48 (d, *J* = 1.3, 1 H); 1.99 (d, *J* = 1.2, 3 H); 1.26 (s, 3 H); 1.23 (s, 3 H).

EXAMPLE 118

(*R/S*)-9-Chloro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **218**, structure **42** of **Scheme XI**, where R=4-chlorophenyl, R^1=H, R^2=Cl)

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **209** (40 mg, 0.12 mmol) and 4-bromochlorobenzene (0.19 g) to afford 23 mg (44%) of

Compound **218** as an off-white oil. Data for Compound **218**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.59 (d, *J* = 2.5, 1 H); 7.58 (d, *J* = 8.4, 1 H); 7.27 (d, *J* = 8.6, 2 H); 7.22 (d, *J* = 8.6, 2 H); 6.96 (dd, *J* = 8.5, 2.4, 1 H); 6.94 (s, 1 H); 6.84 (d, *J* = 8.4, 1 H); 6.78 (d, *J* = 8.5, 1 H); 5.7 (br s, 1 H); 5.49 (d, *J* = 1.1, 1 H); 1.99 (d, *J* = 1.1, 3 H); 1.27 (s, 3 H); 1.24 (s, 3 H).

EXAMPLE 119

(Z)-5-Butylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **219**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=*n*-propyl)

General Method 6: Preparation of compounds of structure **43** from Compound **159** or compounds of structure **39**. This transformation involves the addition of a Grignard reagent (or, alternatively, an organolithium reagent) to Compound **159** or compounds of structure **41** followed by an acid catalyzed dehydration reaction. To a flame-dried flask charged with magnesium powder (8-10 equivuiv) and iodine (1-5%) under nitrogen was added one fourth of a solution of the corresponding benzyl bromide (or chloride) (8-10 equivuiv) in 2-3 mL of THF or ether. The mixture was allowed to stir for 5-10 min until the reaction initiated (a few drops of 1,2-dibromoethane might be necessary to initiate the reaction), and then the rest of the benzyl bromide (chloride) solution was added and the reaction went to completion in several min to give a colorless solution. The Grignard reagent solution was cannulated into a yellow solution of Compound **159** or a compound of structure **41** in 1-2 mL of THF and the resulting dark red mixture was allowed to stir at rt for 20-66 min until the red color faded. The reaction was quenched with water (5 mL) and extracted with ethyl acetate (2 x 15 mL). Removal of the solvent under reduced pressure afforded the crude lactol as a yellow oil, which was dissolved in 5 mL of methylene chloride and was treated with *p*-toluenesulfonic acid (5-10 mol%). The reaction was stirred at rt for 30 min and was quenched with a 2% NaOH aqueous solution (2 mL). The mixture was extracted with ethyl acetate (20 mL) and was washed with brine (5 mL), and was then concentrated. Chromatography of the crude mixture on a silica gel column using 10 % ethyl acetate/hexane as the eluent afforded the compound of structure **45** as a bright yellow oil or solid in good yield.

(Z)-5-Butylidene-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **219**, structure **45** of **Scheme XIII**, where $R^1=R^2=H$, $R^3=n$-propyl) This compound was prepared by General Method 6 from 1.6 M hexane solution of *n*-butyllithium (0.2 mL, 0.32 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 4.8 mg (21%) of Compound **219** as a bright yellow oil. Data for Compound **219**: $R_f = 0.62$ (silica gel, 25% EtOAc: hexane); ^{1}**H NMR** (400 MHz, acetone-d_6) 7.74 (d, *J* = 7.5, 1 H), 7.54 (d, *J* = 8.4, 1 H), 7.14 (t , *J* = 7.5, 1 H), 7.03-6.98 (m, 2 H), 6.74 (d, *J* = 8.4, 1 H), 5.48 (s, 1 H), 4.81 (t, *J* = 7.5, 1 H), 2.40-2.35 (m, 2 H), 2.09 (s, 3 H), 1.49-1.44 (m, 2 H), 1.27 (br s, 6 H), 0.93 (t, *J* = 7.3, 3 H).

EXAMPLE 120

(Z)-5-Benzylidene-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **220**, structure **45** of **Scheme XIII**, where $R^1=R^2=H$, R^3=phenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from benzyl bromide (171 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 6.3 mg (25%) of Compound **220** as a bright yellow oil. Data for Compound **220**: $R_f = 0.50$ (silica gel, 25% EtOAc: hexane); ^{1}**H NMR** (400 MHz, acetone-d_6) 7.82 (t, *J* = 7.6, 3 H), 7.64 (d, *J* = 8.4, 1 H), 7.38 (t , *J* = 7.6, 2 H), 7.24-7.20 (m, 3 H), (7.09-7.06) (m, 1 H), 6.84 (d, *J* = 8.4, 1 H), 5.68 (s, 1 H), 5.55 (s 1 H), 2.11 (s, 3 H), 1.29 (br s, 6 H).

EXAMPLE 121

(Z)-5-(4-Fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **221**, structure **45** of **Scheme XIII**, where $R^1=R^2=H$, R^3=4-fluorophenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 4-fluorobenzyl chloride (145 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 17 mg (63%) of Compound **221** as a bright yellow oil. Data for Compound **221**: $R_f = 0.56$ (silica gel, 25% EtOAc: hexane); ^{1}**H NMR** (400 MHz, acetone-d_6) 7.87-7.82 (m, 3 H), 7.64 (d, *J* = 8.4, 1 H), 7.22-7.05 (m, 5 H), 6.82 (d, *J* = 8.4, 1 H), 5.68 (s, 1 H), 5.54 (s, 1 H), 2.10 (s, 3 H), 1.32 (br s, 6 H).

EXAMPLE 122

(Z)-5-(4-Bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **222**, structure **45** of **Scheme XIII**, where $R^1=R^2=H$, R^3=4-bromophenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 4-bromobenzyl bromide (250 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 24 mg (82%) of Compound **222** as a bright yellow oil. Data for Compound **222**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.83 (d, J = 8.4, 1 H), 7.77 (d, J = 8.6, 2 H), 7.65 (d, J = 8.4, 1 H), 7.55 (d, J = 8.6, 2 H), 7.26-7.17 (m, 2 H), 7.11-7.06 (m, 1 H), 6.84 (d, J = 8.3, 1 H), 5.66 (s, 1 H), 5.55 (s, 1 H), 2.09 (s, 3 H), 1.34 (br s, 6 H).

EXAMPLE 123

(Z)-5-(3-Bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 223, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=3-bromophenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 3-bromobenzyl bromide (250 mg, 1.0 mmol) and Compound **159** (15 mg, 0.05 mmol) to afford 22 mg (98%) of Compound **223** as a bright yellow oil. Data for Compound **223**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.03 (s, 1 H), 7.85 (d, J = 7.9, 1 H), 7.78 (d, J = 7.9, 1 H), 7.66 (d, J = 8.4, 1 H), 7.41-7.17 (m, 4 H), 7.09 (t, J = 7.9, 1 H), 6.85 (d, J = 8.3, 1 H), 5.67 (s, 1 H), 5.55 (s, 1 H), 2.10 (s, 3 H), 1.33 (br s, 6 H).

EXAMPLE 124

(Z)-5-(3-Chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **224**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=3-chlorophenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 3-chlorobenzyl chloride (161 mg, 1.0 mmol) and Compound **159** (10 mg, 0.035 mmol) to afford 6.3 mg (45%) of Compound **224** as a bright yellow oil. Data for Compound **224**: R_f = 0.33 (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 7.88-7.85 (m, 2 H), 7.72 (d, J = 8.0, 1 H), 7.67 (d, J = 8.4, 1 H), 7.40 (t, J = 8.0, 1 H), 7.26-7.20 (m, 3 H), 7.12-7.08 (m, 1 H), 6.85 (d, J = 8.4, 1 H), 5.68 (s, 1 H), 5.56 (s, 1 H), 2.10 (s, 3 H), 1.29 (br s, 6 H).

EXAMPLE 125

(Z)-5-(3-Fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **225**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=3-fluorophenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 3-fluorobenzyl bromide (189 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 5.4 mg (20%) of Compound **225** as a bright yellow oil. Data for Compound **225**: $R_f = 0.50$ (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 7.85 (d, *J* = 7.9, 1 H), 7.66 (d, *J* = 8.6, 2 H), 7.52 (d, *J* = 7.9, 1 H), 7.43-7.38 (m, 1 H), 7.25-7.23(m, 2 H), 7.11-7.07 (m, 1 H), 7.02-6.97 (m, 1 H), 6.85 (d, *J* = 8.6, 1 H), 5.70 (s, 1 H), 5.55 (s, 1 H), 2.10 (s, 3 H), 1.29 (br s, 6 H).

EXAMPLE 126

(Z)-5-(2-Chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **226**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=2-chlorophenyl) This compound was prepared by General Method 6 (EXAMPLE 119) from 2-chlorobenzyl chloride (161 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 8.4 mg (30%) of Compound **226** as a bright yellow oil. Data for Compound **226**: $R_f = 0.44$ (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 8.44 (d, *J* = 7.9, 1 H), 7.85 (d, *J* = 7.9, 1 H), 7.67 (d, *J* = 8.5, 1 H), 7.45-7.37 (m, 2 H), 7.25-7.21(m, 3 H), 7.20-7.11(m, 1 H), 6.86 (d, *J* = 8.5, 1 H), 6.20 (s, 1 H), 5.55 (s, 1 H), 2.15 (s, 3 H), 1.29 (br s, 6 H).

EXAMPLE 127

(Z)-5-(2-Bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **227**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=2-bromophenyl) This compound was prepared by General Method 6 (EXAMPLE 119) from 2-bromobenzyl bromide (250 mg, 1.0 mmol) and Compound **159** (20 mg, 0.07 mmol) to afford 2.8 mg (10%) of Compound **227** as a bright yellow oil. Data for Compound **227**: $R_f = 0.44$ (silica gel, 25% EtOAc: hexane); **^{1}H NMR** (400 MHz, acetone-d_6) 8.45 (d, *J* = 7.9, 1 H), 7.85 (d, *J* = 7.9, 1 H), 7.67 (d, *J* = 8.5, 1 H), 7.64 (d, *J* = 7.9, 1 H), 7.45 (t, *J* = 8.5, 1 H), 7.23 - 7.07 (m, 4 H), 6.87 (d, *J* = 8.5, 1 H), 6.19 (s, 1 H), 5.55 (s, 1 H), 2.15 (s, 3 H), 1.29 (br s, 6 H).

EXAMPLE 128

(Z)-5-(2-Fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **228**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=2-fluorophenyl) This compound was prepared by General Method 6 (EXAMPLE 119) from 2-fluorobenzyl bromide (189 mg, 1.0 mmol) and Compound **159** (10 mg, 0.034 mmol) to afford 2.1 mg (16%) of Compound **228** as a bright yellow oil. Data for Compound **228**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.39 (m, 1 H), 7.85 (d, *J* = 7.4, 1 H), 7.67 (d, *J* = 8.5, 1 H), 7.30-7.06 (m, 6 H), 6.86 (d, *J* = 8.5, 1 H), 5.96 (s, 1 H), 5.90 (s, 1 H), 5.55 (s, 1 H), 2.13 (s, 3 H), 1.32 (br s, 6 H).

EXAMPLE 129

(Z)-5-(2,3-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **229**, structure **45** of **Scheme XIII**, where R^1=R^2=H, R^3=2,3-difluorophenyl) This compound was prepared by General Method 6 (EXAMPLE 119) from 2,3-difluorobenzyl bromide (207 mg, 1.0 mmol) and Compound **159** (10 mg, 0.034 mmol) to afford 4.8 mg (35%) of Compound **229** as a bright yellow oil. Data for Compound **229**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.18 (dd, *J* = 8.0, 6.6, 1 H), 7.87 (d, *J* = 7.5, 1 H), 7.69 (d, *J* = 8.5, 1 H), 7.30-7.08 (m, 5 H), 6.89 (d, *J* = 8.4, 1 H), 5.94 (s, 1 H), 5.57 (s, 1 H), 2.12 (s, 3 H), 1.31 (br s, 6 H).

EXAMPLE 130

(Z)-5-(2,5-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound **230**, structure **45** of **Scheme XII**, where R^1=R^2=H, R^3=2,5-difluorophenyl) This compound was prepared by General Method 6 (EXAMPLE 119) from 2,5-difluorobenzyl bromide (207 mg, 1.0 mmol) and Compound **159** (15 mg, 0.05 mmol) to afford 17 mg (82%) of Compound **230** as a bright yellow oil. Data for Compound **230**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.12 (m, 1 H), 7.88 (d, *J* = 8.3, 1 H), 7.69 (d, *J* = 8.5, 1 H), 7.30-7.00 (m, 5 H), 6.89 (d, *J* = 8.4, 1 H), 5.93 (s, 1 H), 5.94 (s, 1 H), 5.56 (s, 1 H), 2.11 (s, 3 H), 1.32 (br s, 6 H).

EXAMPLE 131

(Z)-9-Fluoro-5-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 231, structure **45** of Scheme XIII, where R^1=H, R^2=F, R^3=3-fluorophenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 3-fluorobenzyl chloride (0.17 g) and Compound **207** (31 mg) to afford 7.5 mg (19%) of Compound **231** as a yellow oil. Data for Compound **231**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.65 (d, *J* = 8.4, 1 H), 7.64 (m, 1 H); 7.60 (dd, *J* = 10.0, 3.0, 1 H); 7.52 (d, *J* = 7.6, 1 H); 7.40 (m, 1 H); 7.26 (dd, *J* = 8.9, 4.8, 1 H); 7.00 (m, 2 H); 6.86 (d, *J* = 8.3, 1 H); 5.72 (s, 1 H); 5.57 (d, *J* = 1.2, 1 H); 2.10 (s, 3 H), 1.40 (br s, 6 H).

EXAMPLE 132

(Z)-9-Fluoro-5-(3-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 232, structure **45** of Scheme XIII, where R^1=H, R^2=F, R^3=3-methoxylphenyl)

This compound was prepared by General Method 6 (EXAMPLE 119) from 3-methoxylbenzyl chloride (0.18 g) and Compound **207** (31 mg) to afford 11 mg (27%) of Compound **232** as a yellow oil. Data for Compound **232**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.63 (d, *J* = 5, 1 H); 7.58 (dd, *J* = 10.0, 2.9, 1 H); 7.48 (br s, 1 H); 7.28 (d, *J* = 5.1, 2 H); 7.22 (m, 1 H); 6.98 (m, 1 H); 6.83 (d, *J* = 9.6, 1 H); 6.82 (m, 1 H); 5.68 (s, 1 H); 5.56 (s, 1 H); 3.86 (s, 3 H); 2.10 (s, 3 H); 1.35 (br s, 6 H).

EXAMPLE 133

(Z)-8-Fluoro-5-(3-fluororbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 233, structure **45** of Scheme XIII, where R^1=F, R^2=H, R^3=3-fluorophenyl) This compound was prepared by General Method 6 (EXAMPLE 119) from 3-fluorobenzyl chloride (0.17 g) and Compound **208** (31 mg) to afford 7.5 mg (19%) of Compound **233** as a yellow oil. Data for Compound **233**: ^{1}**H NMR** (400 MHz, acetone-d_6) 7.88 (dd, *J* = 9.7, 6.2, 1 H); 7.63 (d, *J* = 8.5, 1 H); 7.58 (m, 2 H); 7.42 (dd, *J* = 8.0, 6.4, 1

H); 7.09 (dd, *J* = 9.5, 2.7, 1 H); 7.00 (m, 1 H); 6.92 (m, 1 H); 6.85 (d, *J* = 8.2, 1 H); 5.73 (s, 1 H); 5.63 (s, 1 H); 2.10 (s, 3 H); 1.35 (br s, 6 H).

EXAMPLE 134

(*R*/*S*-4*l*, 5*u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound **234**, structure **52** of **Scheme XV**, where R=4-chlorophenyl, R^1=R^2=H)

This compound was prepared by a four step procedure as depicted in **Scheme XV**. To a yellow solution of Compound **163** (EXAMPLE 63) (120 mg, 0.3 mmol) in THF (6 mL) at -78°C was added 0.3 mL of *n*-BuLi (1.6 M in hexane, 0.48 mmol), and the resulting solution was stirred for 15 min before a solution of di-*t*-butyl dicarbonate (150 mg, 0.7 mmol) in 2 mL of THF was introduced. The reaction mixture was allowed to warm up to rt and was stirred for 5 h. The mixture was quenched with water and was extracted with ethyl acetate (2 x 20 mL). Removal of solvent and chromatography of the crude mixture on a silica gel column using 10-30% mixture of ethyl acetate and hexane afforded 50 mg (34%) of the *t*-Boc protected quinoline (structure **49** of **Scheme XV** where R=4-chlorophenyl, R^1=R^2=H) and 80 mg (66%) of Compound **163**.

The *t*-Boc protected Compound **163** (structure **49** of **Scheme XV** where R=4-chlorophenyl, R^1=R^2=H) (40 mg, 0.08 mmol) in THF (4 mL) was treated with 0.3 mL of BH_3.THF (1.0 M in THF, 0.3 mmol) at rt for 3 h and was then quenched with 0.2 mL of KOH (3 M aqueous). To the above solution 0.2 mL of H_2O_2 (30% in water) was added and the mixture was stirred for 30 min, then 5 mL of water was introduced. The mixture was extracted with EtOAc, washed with brine and concentrated. Chromatography of the crude mixture on a silica gel column (10-30% EtOAc/hexane gradient) afforded two major isomers. The first fraction (20 mg, 50%) was assigned as (*R*/*S*-3*l*, 4*u*, 5*l*)-1-*t*-butyloxycarbonyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (structure **50** of **Scheme XV** where R=4-chlorophenyl, R^1=R^2=H). The second fraction (12 mg, 30%) was assigned as (*R*/*S*-3*l*, 4*u*, 5*u*)-1-*t*-butyloxylcarbonyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-

chromeno[3,4-*f*]quinoline (structure **51** of **Scheme XV** where R=4-chlorophenyl, $R^1=R^2=H$).

(*R/S*-3*l*, 4*u*, 5*l*)-1-*t*-Butyloxylcarbonyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (structure **50** of **Scheme XV** where R=4-chlorophenyl, $R^1=R^2=H$) (20 mg, 0.04 mmol) was oxidized with PCC (100 mg, 0.46 mmol) in 5 mL of methylene chloride at rt for 60 min to yield (*R/S*-4*l*, 5*u*)-1-*t*-butyloxylcarbonyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone as a colorless oil after chromatography. This compound was then treated with 0.2 mL of TFA in 0.5 mL of methylene chloride for 30 min and was quenched with 5 mL of KOH (2%). The reaction mixture was extracted with EtOAc, washed with brine and was concentrated. Chromatography of the crude residue on a silica gel column (10-30% EtOAc/hexane gradient) afforded 15 mg (93%) of Compound **234** as a white solid. Data for Compound **234**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.64 (d, *J* = 8.2, 2 H), 7.18 (d, *J* = 8.6, 2 H), 7.13 (d, *J* = 8.6, 2 H), 7.05 (t, *J* = 7.9, 1 H), 6.96 (t, *J* = 7.8, 1 H), 6.84 (d, *J* = 8.3, 1 H), 6.76 (d, *J* = 7.9, 1 H), 6.37 (s, 1 H), 3.73 (s, 1 H), 3.56 (q, *J* = 7.4, 1 H), 1.44 (s, 3 H), 1.26 (s, 3 H), 0.87 (d, *J* = 7.4, 3 H).

EXAMPLE 135

(*R/S*-4*l*, 5*l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound **235**, structure **53** of **Scheme XV**, where R=4-chlorophenyl, $R^1=R^2=H$)

(*R/S*-3*l*, 4*u*, 5*u*)-1-*t*-Butyloxylcarbonyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (structure **51** of **Scheme XV** where R=4-chlorophenyl, $R^1=R^2=H$) (EXAMPLE 134) (12 mg, 0.024 mmol) was oxidized and deprotected by methods similar to that described for Compound **234** (EXAMPLE 134) to yield 8 mg (84%) of Compound **235** as a white solid. Data for Compound **235**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.59 (d, *J* = 8.4, 1 H), 7.57 (d, *J* = 8.0, 1 H), 7.15 (d, *J* = 8.5, 2 H), 7.06 (d, *J* = 8.5, 2 H), 7.04 (m, 1 H), 6.94 (t, *J* = 7.8, 1 H), 6.85 (d, *J* = 7.6, 1 H), 6.83 (d, *J* = 8.3, 1 H), 3.73 (s, 1 H), 3.35 (d, *J* = 7.5, 1 H), 1.50 (d, *J* = 7.5, 3 H), 1.46 (s, 3 H), 1.17 (s, 3 H).

EXAMPLE 136

(*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,4-tetramethyl-*5H*-chromeno[3,4-*f*]-3-quinolinone (Compound **236**, structure **54** of Scheme **XV** where R=4-chlorophenyl, R^1=R^2=H)

To a solution of (*R/S-4l, 5u*)-1-*t*-butyloxylcarbonyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]-3-quinolinone (EXAMPLE 234) (5 mg, 0.01 mmol) in 2 mL of THF was added 10 mg of NaH (40% in mineral oil, 0.25 mmol) and the resulting slurry was stirred at rt for 20 min before MeI (0.1 g, 0.7 mmol) was introduced. The mixture was stirred at rt for 2 h and was then quenched with water (5 mL). The mixture was extracted with EtOAc and purified by silica gel chromatography to provide 1.5 mg (36%) of Compound **236** as a colorless oil. Data for Compound **236**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.59 (d, *J* = 8.2, 1 H), 7.56 (d, *J* = 7.8, 1 H), 7.13 (d, *J* = 8.7, 2 H), 7.09 (d, *J* = 8.7, 2 H), 7.01 (t, *J* = 7.9, 1 H), 6.91 (t, *J* = 7.9, 1 H), 6.85 (s, 1 H), 6.83-6.78 (m, 2 H), 3.83 (s, 1 H), 1.63 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H).

EXAMPLE 137

1,2-Dihydro-2,2,4-trimethyl-6-methoxymethyl-8-pyranono[5,6-*g*]quinoline (Compound **237**, structure **57** of Scheme **XVI**, where R^1=R^2=H, R^3=methoxylmethyl, Y=O)

General Method 7: 1,2-Dihydro-2,2,4-trimethylquinolines (Compounds of structure **57** or **67**) from anilines (Compounds of structure **56** or **66**): ambient pressure version In an r.b. flask equivuipped with a reflux condensor, a solution of the aniline (a compound of structure **56** or **66**) in acetone (0.05-0.20 M) was treated with iodine (5-20 mol%) and heated to reflux for 1-3 days. Addition of Celite™ followed by concentration afforded a fluffy orange powder which was purified by silica gel chromatography to afford the desired dihydroquinoline (compound of structure **57** or **67**).

1,2-Dihydro-2,2,4-trimethyl-6-methoxymethyl-8-pyranono[5,6-*g*]quinoline (Compound **237**, structure **57** of Scheme **XVI**, where R^1=R^2=H, R^3=methoxylmethyl, Y=O) This compound was prepared by General Method 7 from 7-amino-4-methoxymethylcoumarin (structure **56** of **Scheme XVI**, where R^1=R^2=H, R^3=methoxymethyl) (1.0 g, 4.87 mmol) to afford 82 mg (6%) of Compound **237** as a light yellow solid in addition to 487 mg (35%) of

1,2-dihydro-2,2,4-trimethyl-8-methoxymethyl-6-pyranono[6,5-*f*]quinoline. Data for Compound **237**: R_f 0.23 (silca gel, hexanes/EtOAc, 2:1); **^{1}H NMR** (400 MHz, C_6D_6) 7.01 (s, 1 H), 6.24 (s, 1 H), 6.18 (s, 1 H), 5.02 (s, 1 H), 3.97 (s, 2 H), 3.74 (br s, 1 H), 2.92 (s, 3 H), 1.78 (d, *J* = 1.0, 3 H), 0.98 (s, 6 H).

EXAMPLE 138

1,2-Dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **238**, structure **57** of **Scheme XVII**, where R^1=R^2=H, R^3=trifluoromethyl, Y=O) This compound was prepared as depicted in **Scheme XVII** and as described below.

O-Pivaloyl-3-nitrophenol (structure **65** of **Scheme XVII**, where R^1=H, P=*t*-butyl, Y=O) To 300 mL of CH_2Cl_2 was added 3-nitrophenol (structure **64** of **Scheme XVII**, where R^1=H, Y=O) (15 g, 0.11 mol), pyridine (20 mL) and DMAP (10 mg). To this cooled solution (0°C) was slowly added trimethylacetyl chloride (18 mL, 146 mmol, 1.4 equivuiv). The solution was allowed to warm to rt and stirred for 3 h. To the amber colored solution was added sat'd NH_4Cl (300 mL). The organic layer was washed with 1N HCl (2 x 150 mL), 10% $CuSO_4 \cdot 5\,H_2O$ (2 x 100 mL), and brine (2 x 100 mL). The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give 22.5 g (94%) of *O*-pivaloyl-3-nitrophenol as a white solid. Data for *O*-pivaloyl-3-nitrophenol: R_f 0.55 (silica gel, hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 8.11 (dd, *J* = 4.2, 1.3, 1 H), 7.96 (t, *J* = 2.2, 1 H), 7.56 (dd, *J* = 8.4, 8.2, 1 H), 7.42 (dd, *J* = 6.5, 1.3, 1 H), 1.35 (s, 9 H).

O-Pivaloyl-3-aminophenol (structure **66** of **Scheme XVII**, where R^1=H, P=*t*-butyl, Y=O) To 60 mL anhydrous CH_2Cl_2 was added *O*-pivaloyl-3-nitrophenol (5.0 g, 22.4 mmol) and a catalytic amount (50 mg) of 10% Pd on C. The flask was repeatedly evacuated and flushed with N_2. The reaction flask was again evacuated and H_2 was introduced by balloon. After stirring under an atmosphere of H_2 for 3 h, the reaction flask was flushed twice with N_2. The suspension was then filtered through a bed of Celite™ and concentrated to give 4.15 g (96%) of *O*-pivaloyl-3-aminophenol as a viscous amber oil. Data for *O*-pivaloyl-3-aminophenol: R_f 0.21 (silica gel, hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.12 (dd, *J* = 8.0, 8.0, 1 H), 6.52 (dd, *J* = 7.8, 2.7, 1 H), 6.44 (ddd, *J* = 8.0, 2.4, 1.4, 1H), 6.38 (t, *J* = 2.2, 1 H), 3.81 (br s, 2 H), 1.34 (s, 9 H).

General Method 8. 1,2-Dihydro-2,2,4-trimethylquinolines (Compounds of structure **57** or **67**) from anilines (Compounds of structure **56** or **66**); pressure tube version In a threaded resealable pressure tube, a solution of the aniline (a compound of structure **56** or **66**) in acetone (0.05-0.20M) was treated with iodine (5-20 mol%) and heated to 100-120 °C for 1-3 days. The reaction vessel was allowed to cool to rt and transferred to a r.b. flask. Addition of Celite™ followed by concentration afforded a fluffy orange powder which was purified by silica gel chromatography to afford the desired dihydroquinoline (Compound of structure **57** or **67**).

1,2-Dihydro-2,2,4-trimethyl-7-(1,1,1-trimethylacetoxy)quinoline (structure **67** of **Scheme XVII**, where R^1=H, P=*t*-butyl, Y=O This compound was prepared by General Method 8 from *O*-pivaloyl-3-aminophenol (structure **66** of **Scheme XVII**, where R^1=H, P=*t*-butyl, Y=O) (1.26 g, 6.53 mmol) to afford 1.06 g (60%) of 1,2-dihydro-2,2,4-trimethyl-7-(1,1,1-trimethylacetoxy)quinoline as a light brown solid. Data for 1,2-dihydro-2,2,4-trimethyl-7-(1,1,1-trimethylacetoxy)quinoline: R_f 0.23 (silica gel, hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.00 (d, *J* = 8.3, 1 H), 6.28 (dd, *J* = 5.2, 2.3, 1 H), 5.25 (s, 1 H), 3.69 (s, 1 H,), 1.96 (d, *J* = 1.2, 3 H), 1.32 (s, 9 H), 1.26 (s, 6 H).

1,2-Dihydro-7-hydroxy-2,2,4-trimethylquinoline To 70 mL 85% ethanol was added 1,2-dihydro-2,2,4-trimethyl-7-(1,1,1-trimethylacetoxy)quinoline (1.03 g, 3.77 mmol) and 20% NaOH(aq) (3 mL) to give a clear colorless solution. The reaction was followed by TLC (hexanes/EtOAc, 3:1). After 3 h the resulting purple solution was quenched with sat'd NH_4Cl (200 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (2 x 75 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a dark purple oil. The oil was dissolved in a minimal amount of hexanes / ethyl acetate (3:1), and filtered though a plug of silica rinsing with a solution of hexanes / ethyl acetate (3:1). The washes were concentrated *in vacuo* to afford 710 mg (99%) of 1,2-dihydro-7-hydroxy-2,2,4-trimethylquinoline as a dark yellow oil. Data for 1,2-dihydro-7-hydroxy-2,2,4-trimethylquinoline: R_f 0.30 (silica gel, hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, DMSO-d_6) 8.90 (s, 1 H), 6.70 (d, *J* = 8.2, 1 H), 5.89 (d, *J* = 2.3, 1 H), 5.85 (dd, *J* = 8.3, 2.4, 1 H), 5.65 (s, 1 H), 5,04 (s, 1 H), 1.8 (d, *J* = 1.1, 3 H), 1.14 (s, 6 H).

1,2-Dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline(Compound **238**, structure **57** of **Scheme XVII**, where R^1=R^2=H, R^3=trifluoromethyl, Y=O)

General Method 9: Preparation of Compounds of structure **56** or **57** from phenols. To a solution of 1,2-dihydro-7-hydroxy-2,2,4-trimethylquinoline (0.1-0.5 M) in absolute EtOH was added a β-keto ester (a compound of structure **68**) (1-3 equivuiv) in a 4 x 13.5 cm pressure tube equivuipped with a magnetic stir bar and a threaded Teflon stopcock. To this solution was added $ZnCl_2$ (1-6 equivuiv). The sealed pressure tube was heated in a oil bath at 80-120 °C for 6-72 h. The cooled solution was diluted with sat'd NH_4Cl and extracted with ethyl acetate. The combined organics were concentrated on Celite™ under reduced pressure to give a free flowing powder, which was purified by flash column chromatography (silica gel 60, hexanes / ethyl acetate, 5:1) to give the desired product. Further purification could be effected by recrystallization from hexanes / toluene.

1,2-Dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline(Compound **238**, structure **55** of **Scheme XVII**, where R^1=R^2=H, R^3=trifluoromethyl, Y=O) This compound was prepared by General Method 9 from 1,2-dihydro-7-hydroxy-2,2,4-trimethylquinoline (1.58 g, 8.5 mmol) and ethyl 4,4,4-trifluoroacetoacetate (3.00 g, 16.8 mmol, 2.0 equivuiv) to afford 1.7 g (66%) of Compound **238** as a light yellow powder. Data for Compound **238**: R_f 0.32 (silica gel, hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, C_6D_6) 7.22 (s, 1 H), 6.15 (s, 1H), 5.97 (s, 1 H), 4.93 (s, 1 H), 3.23 (br s, 1 H), 1.66 (d, *J* = 1.1, 3 H), 0.98 (s, 6 H).

EXAMPLE 139

1,2-Dihydro-2,2,4-trimethyl-10-isocoumarino[4,3-*g*]quinoline (Compound **239**, structure **57** of **Scheme XVI**, where R^1H, R^2=R^3=benzo, Y=O)

This compound was prepared by General Method 8 (EXAMPLE 138) from 7-amino-3,4-benzocoumarin (structure **56** of **Scheme XVI**, where R^1=H, R^2=R^3=benzo, Y=O) (180 mg, 0.85 mmol) to afford 75 mg (30%) of Compound **239** along with 150 mg (60%) of 1,2-dihydro-2,2,4-trimethyl-10-isocoumarino[3,4-*f*]quinoline as yellow solids. Data for Compound **239**: mp 246-248 °C; ^{1}**H NMR** (400 MHz, $CDCl_3$) 8.18 (d, *J* = 7.6, 1 H), 8.16

(d, *J* = 7.6, 1 H), 7.80 (s, 1 H), 7.78 (t, *J* = 7.6, 1 H), 7.43 (t, *J* = 7.6, 1 H), 6.39 (s, 1 H), 5.45 (s, 1 H), 2.11 (s, 3 H), 1.33 (s, 6 H), **^{13}C NMR** (100 MHz, $CDCl_3$) 162.2, 152.7, 146.1, 136.4, 134.9, 130.7, 129.1, 127.2, 126.5, 120.5, 119.4, 119.0, 117.8, 107.6, 99.8, 52.7, 31.8, 19.0; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.99; H, 5.79; N, 4.72.

EXAMPLE 140

1,2-Dihydro-2,2,4-trimethyl-10-isoquinolono[4,3-*g*]quinoline(Compound **240**, structure **57** of **Scheme XVI**, where R^1=H, R^2=R^3=benzo, Y=NH)

3-Amino-6(*5H*)-phenanthridinone (structure **56** of **Scheme XVI**, where R^1=H, R^2=R^3=benzo, Y=NH) A mixture of 3-nitro-6(*5H*)-phenanthridinone (structure **55** of **Scheme XVI**, where R^1=H, R^2=R^3=benzo, Y=NH) (480 mg, 1.5 mmol) and 50 mg of 10% Pd/C in 60 mL of DMF was stirred under an atomsphere of H_2 for 2 h. The mixture was filtered through a Celite™ pad and the filtrate was concentrated to give 0.4 g of the crude aniline as a yellow solid. This material was used without further purification.

1,2-Dihydro-2,2,4-trimethyl-10-isoquinolono[4,3-*g*]quinoline (Compound **240**, structure **57** of **Scheme XVI**, where R^1=H, R^2=R^3=benzo, Y=NH) This compound was prepared by General Method 8 (EXAMPLE 238) from 3-amino-6(*5H*)-phenanthridinone (0.4 g), iodine (150 mg, 0.6 mmol), acetone (16 mL) and DMF (14 mL) to afford 220 mg (51%) of Compound **240** as a yellow solid. Data for Compound **240**: mp 301-302 °C; **IR** (KBr, cm^{-1}) 3300, 3010, 1670, 1450, 1300; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.28 (d, *J* = 7.6, 1 H), 8.25 (d, *J* = 7.6, 1 H), 7.90 (s, 1 H), 7.70 (t, *J* = 7.6, 1 H), 7.39 (t, *J* = 7.6, 1 H), 6.48 (s, 1 H), 5.78 (br s, 1 H), 5.42 (s, 1 H), 2.13 (s, 3 H), 1.33 (s, 6 H); **^{13}C NMR** (100 MHz, acetone-d_6) 162.4, 147.1, 139.2, 137.0, 133.3, 129.2, 128.7, 128.6, 125.8, 125.0, 121.8, 118.9, 118.4 108.5, 98.1, 52.8, 31.6, 19.0.

EXAMPLE 141

1,2-Dihydro-2,2,4,6-tetramethyl-8-pyridono[5,6-*g*]quinoline (Compound **241**, structure **57** of **Scheme XVI**, where R^1=R^2=H, R^3=methyl, Y=NH)